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ABSTRACT

Six times since 1964, the Public Health Service has issued formal reviews of the scientific evidence which links cigarette smoking to disease and premature death. Each successive review, including this one, has seemed to confirm and strengthen the conclusion of the 1964 Report, that cigarettes are a major cause of death and disease. In the first three chapters of this report, the relationships between cigarette smoking and cancer, cardiovascular disease, and non-neoplastic bronchopulmonary disease are reviewed and evidence is presented which helps develop our understanding of the mechanisms which are involved in these relationships. In the final three chapters, information is presented on public exposure to air pollution from tobacco, on the relationship between tobacco and allergy, and on the harmful consituents which are found in cigarette smoke. The chapter which discusses the harmful constituents of smoke is a useful statement of our current knowledge in this field. (Author)

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The
Health Consequences
# of SMOKING

A REPORT OF THE SURGEON GENERAL: 1972

CG 007 561

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The
Health Consequences of Smoking

A Report of the Surgeon General: 1972

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Health Services and Mental Health Administration

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Honorable Carl Albert
Speaker of the House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

Enclosed is the 1972 report on the health consequences of smoking, as called for by Section 8(a) of the Public Health Cigarette Smoking Act of 1969. As you will see, it continues and strengthens the findings of previous Public Health Service reports that cigarette smoking is a hazard to the health of the American people.

Under this Act, I am also required to submit to you such recommendations for legislation as I deem appropriate.

As you know, it has long been the position of this Department that an adequate health warning should appear in cigarette advertisements along with listings of "tar" and nicotine. We are in support of the current efforts of the Federal Trade Commission to bring this about through the exercise of its regulatory powers. Should these efforts fail, however, we would return to our previous recommendations that this should be accomplished through legislative action.

With kindest regards,

Sincerely,

Elliot L. Richardson
Secretary

Preface

Six times since 1964, the Public Health Service has issued formal reviews of the scientific evidence which links cigarette smoking to disease and premature death. Each successive review, including this one, has served to confirm and strengthen the conclusion of the 1964 Report, that cigarettes are a major cause of death and disease.

In the first three chapters of this report, the relationships between cigarette smoking and cancer, cardiovascular disease, and non-neoplastic bronchopulmonary disease are reviewed and evidence is presented which helps develop our understanding of the mechanisms which are involved in these relationships. In the final three chapters, information is presented on public exposure to air pollution from tobacco, on the relationship between tobacco and allergy, and on the harmful constituents which are found in cigarette smoke.

In the past few years, millions of Americans have stopped smoking because they have persuaded themselves that it is in their own self-interest to do so; we must continue to encourage cessation as the only certain way to protect both the individual and society from the harmful effects of smoking. We must also, however, work towards reducing the dangers of smoking for those who have not quit by developing less hazardous cigarettes and encouraging less hazardous ways of smoking. The chapter which discusses the harmful constituents of smoke is a useful statement of our current knowledge in this field; it should interest not only research scientists but those who are concerned with public education and public policy.

Research in smoking and health continues, as this report shows, both in this country and abroad and under both public and private auspices; furthermore, the range of this research is widening as the significance of cigarette smoking as a public health problem becomes more apparent. In establishing the present series of reports, first under Public Law 89–92 and now under Public Law 91–222, the Congress has given us a means of encouraging the research we need and of building a better understanding of the problem.

JESSE L. STEINFELD, M.D.
Surgeon General

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Preparation of the Report and Acknowledgments

"Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service"* was published in 1964. The following documents were subsequently published as reviews of the medical literature as called for by Public Law 89–92.

1. "The Health Consequences of Smoking, A Public Health Service Review: 1967"**
2. "The Health Consequences of Smoking, 1968 Supplement to the 1967 PHS Review"**
3. "The Health Consequences of Smoking, 1969 Supplement to the 1967 PHS Review"**

These documents reviewed the medical literature which had been published since the original Surgeon General's Report. The format of publishing a supplement to a supplement became unwieldy, particularly in the light of the lack of availability of previous reviews to the general public. Therefore, when P.L. 91–222 was signed into law on April 1, 1970, calling for an 18-month interval between the previous report and the new report, the entire field was reviewed with an emphasis on the most recent additions to the literature. The product of this review was: "The Health Consequences of Smoking, A Report of the Surgeon General: 1971."**

The present document, "The Health Consequences of Smoking, A Report of the Surgeon General: 1972," includes a review of the literature which has been published since the 1971 Report was completed. It also includes an evaluation of the state of knowledge in three areas which have not been previously reviewed in these reports: allergy and tobacco, public exposure to air pollution from tobacco smoke, and harmful constituents of cigarette smoke.

The National Clearinghouse for Smoking and Health has the responsibility for the continuous monitoring and compilation of the medical literature on the health consequences of smoking and for the preparation of this document. This is accomplished through several mechanisms:

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* Referred to in this manuscript as the Surgeon General's Report.

** Referred to in this manuscript as "The Health Consequences of Smoking."

1. An information science corporation is on contract to extract articles on smoking and health from the medical literature of the world. This organization provides a semi-monthly accessions list with abstracts and copies of the various articles. Translations are called for as needed. Articles are classified according to subject and filed by a series of code words and phrases.
2. The National Library of Medicine, through the Medlars system, sends the National Clearinghouse for Smoking and Health a monthly listing of articles in the smoking and health area. These are reviewed, and articles not identified by the information science corporation are ordered.
3. Staff members review current medical literature and identify pertinent articles.

Initial drafts of the present review were prepared by the staff director, assistant staff director, and consulting editors. The first drafts of the individual chapters were sent to experts for review, criticism, and comment with respect to the articles reviewed, articles not included, and conclusions. The drafts were then revised until they met with the general approval of the reviewers. The final drafts were reviewed as a whole by the Director of the National Clearinghouse for Smoking and Health, the Director of the National Cancer Institute, the Director of the National Heart and Lung Institute, the Director of the National Institute of Environmental Health Sciences, and by six additional experts both within and outside of the Public Health Service.

Acknowledgments

The National Clearinghouse for Smoking and Health, Daniel Horn, Ph. D., Director, was responsible for the preparation of this report. Staff Director for the report was John H. Holbrook, M.D., and Assistant Staff Director was Elvin E. Adams, M.D. Daniel P. Asnes, M.D., and David G. Cook, M.D., were Consulting Editors.

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The chapter on Harmful Constituents of Cigarette Smoke was prepared somewhat differently from the rest of the report, being the culmination of a one-day conference held in June 1970 to review this area of knowledge and to discuss a draft report prepared in advance by staff of the National Institute of Environmental Health Sciences and the National Clearinghouse for Smoking and Health. Earlier in this section, some of these participants are acknowledged as contributors to other parts of the report, namely, Dr. Daniel Horn, who served as Chairman of the meeting, Drs. Daniel P. Asnes, Fred G. Bock, Dietrich Hoffmann, Albert C. Kolbye, Gardner C. McMillan, Umberto Saffiotti, Leonard Schuman, Benjamin L. Van Duuren, and Ernest L. Wynder.

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CHAPTER 1

Introduction and Summary

INTRODUCTION AND SUMMARY

Cigarette smoking continues to be a major health problem in the United States today. It is still too early to tell whether the increasing rate of giving up smoking by adults during the years 1967, 1968, 1969, and early 1970 and the plateauing of this effect during the past year have had any measurable effect on the morbidity and mortality associated with smoking. At the same time that the major health professions, voluntary health agencies, and public service agencies concerned have joined with government agencies to reduce the magnitude of this problem through education, research efforts devoted to understanding how cigarette smoking affects biological function to produce disease continue at a high level.

This report is largely concerned with reviewing the research reports which have become available in the past year. In this chapter, brief summary statements are presented of the state of knowledge in several areas. These are followed, where appropriate, by a "highlight" statement of significant additions to knowledge made as a result of the new research presented in greater detail in the body of the report.

The state of knowledge in three areas, which have not been reviewed previously, is also presented in the report. These areas are: Allergy, Public Exposure to Air Pollution from Tobacco Smoke, and the Harmful Constituents of Cigarette Smoke.

SUMMARY: CORONARY HEART DISEASE

Cigarette smokers have higher death rates from coronary heart disease (CHD) than nonsmokers. This relationship is stronger for men than women. Cigarette smoking markedly increases an individual's susceptibility to earlier death from CHD. Cigarette smoking, hypertension, and elevated serum cholesterol are major risk factors contributing to the development of CHD; cigarette smoking acts both independently and conjointly with these other factors to increase the risk of developing CHD. Cigarette smoking may contribute both to the development of CHD and to the exacerbation of preexistent CHD; both nicotine and carbon monoxide are thought to contribute to these abnormal processes. Cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries. Cessation of smoking is associated with a decreased risk of death from CHD. The risk of CHD incurred by pipe and cigar smokers is appreciably less than that incurred by cigarette smokers.

Highlights of 1972 Report: Coronary Heart Disease

1. Recent epidemiological studies from several countries confirm that cigarette smoking is one of the major risk factors contributing to the development of CHD. Avoidance of cigarette smoking is of importance in the primary prevention of CHD.
2. Studies in man and animals have shown a greater myocardial arteriole wall thickness in smokers than nonsmokers.
3. Experimental and epidemiological investigations implicate the elevation of carboxyhemoglobin levels in smokers as a contributor to the development of CHD and arteriosclerotic peripheral vascular disease.
4. Cigarette smoking is considered to be the major cause of pulmonary heart disease (cor pulmonale) in the United States in that it is the most important cause of chronic non-neoplastic bronchopulmonary diseases. Avoidance of cigarette smoking is of importance in the primary prevention of pulmonary heart disease.

SUMMARY: CEREBROVASCULAR DISEASE

Cigarette smokers have higher death rates from cerebrovascular disease than nonsmokers.

SUMMARY: NONSYPHILITIC AORTIC ANEURYSM*

Cigarette smokers have higher death rates from nonsyphilitic aortic aneurysm than nonsmokers.

SUMMARY: PERIPHERAL VASCULAR DISEASE

Cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking appears to aggravate preexistent peripheral vascular disease.

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* This summary statement is the same as that appearing in previous reports, because new studies adding to the understanding of this area have not appeared. Consequently, the literature in this area is not reviewed and the statement is only included to complete this summary chapter.

SUMMARY: NON-NEOPLASTIC BRONCHOPULMONARY DISEASES

Cigarette smoking is the most important cause of chronic obstructive bronchopulmonary disease (COPD) in the United States. Cigarette smokers have higher death rates from pulmonary emphysema and chronic bronchitis and more frequently have impaired pulmonary function and pulmonary symptoms than nonsmokers. Ex-cigarette smokers have lower death rates from COPD than do continuing smokers. Cessation of smoking is associated with improved ventilatory function and decreased pulmonary symptom prevalence. For most of the United States population, cigarette smoking is a more important cause of COPD than air pollution or occupational exposure; cigarette smoking may also act conjointly with occupational or environmental exposure to produce greater COPD morbidity and mortality. An infrequent genetic error, homozygous alpha$_1$-antitrypsin deficiency, has been commonly associated with the early development of severe, panacinar emphysema. Whether or not cigarette smoking acts together with the homozygous or heterozygous deficiency states to increase the risk of developing either panacinar emphysema or the more common forms of COPD has not been adequately studied. Cigarette smoking exerts an adverse effect on the pulmonary clearance mechanism. Respiratory infections are more prevalent and severe among cigarette smokers, particularly among heavy smokers, than among nonsmokers. The risk of developing or dying from COPD among pipe or cigar smokers is probably higher than that among nonsmokers but is clearly less than that among cigarette smokers.

Highlights of the 1972 Report: Non-neoplastic Bronchopulmonary Diseases

1. Recent epidemiological and clinical studies from several countries confirm that men and women cigarette smokers have an increased prevalence of respiratory symptoms and have diminished pulmonary function compared to nonsmokers.
2. Investigations of high school students have demonstrated that abnormal pulmonary function and pulmonary symptoms are more common in smokers than nonsmokers.
3. Recent occupational studies confirm that cigarette smoking is an important cause of COPD, acting both independently and in combination with occupational exposure.
4. Recent experimental studies confirm that cigarette smoking exerts an adverse effect on pulmonary clearance and macrophage function.

5. Pulmonary macrophages obtained from cigarette smokers exhibit characteristic morphologic differences when compared to those obtained from nonsmokers.

SUMMARY: CANCER

Cigarette smoking is the major cause of lung cancer in men and a significant cause of lung cancer in women. The risk of developing lung cancer in both men and women is directly related to an individual's exposure as measured by the number of cigarettes smoked, duration of smoking, earlier initiation, depth of inhalation, and the amount of "tar" produced by the cigarette. The risk of developing lung cancer diminishes with cessation of smoking. Smokers of pipes or cigars have a lower risk of developing lung cancer than cigarette smokers. Certain occupations are associated with an increased risk of developing lung cancer. In these occupational settings cigarette smoking appears to exert an effect that produces much higher lung cancer rates than those resulting either from the occupational exposure alone or from smoking alone. Factors associated with urban living result in an increase in the risk of developing lung cancer; this effect, however, is minor compared to the overriding effect of cigarette smoking.

The smoking of cigarettes, pipes, and cigars is a significant factor in the development of cancers of the larynx and oral cavity. Pipe smoking is causally related to cancer of the lip. The significant association between smoking and the development of cancer of the esophagus is somewhat stronger for cigarettes than for pipes or cigars and the combined exposure to alcohol and cigarettes is associated with especially high rates of cancer of the esophagus. Cigarette smoking is associated with cancer of the urinary bladder in men. There is also an association between cigarette smoking and cancer of the pancreas.

Highlights of the 1972 Report: Cancer

1. Preliminary results from a major prospective epidemiological study in Japan demonstrate a strong association between cigarette smoking and lung cancer. A dose-response relationship was demonstrated for the number of cigarettes smoked. These findings in an Asian population with distinct genetic and cultural characteristics confirm the major importance of cigarette smoking in the causation of lung cancer, a conclusion which up to now has been based largely on studies of Caucasian populations in the United States, Canada, and Europe.

2. Ex-smokers have significantly lower death rates for lung cancer than continuing smokers. The decline in risk following cessation appears to be rapid both for those who have smoked for long periods of time and for those with a shorter smoking history, with the sharpest reductions taking place after the first two years of cessation.
3. The risk of developing lung cancer appears to be higher for smokers who have chronic bronchitis. Though both conditions are directly related to the amount and duration of smoking, an additional risk for lung cancer appears to exist for cigarette smokers with chronic bronchitis which is independent of age and number of cigarettes consumed.
4. Experimental studies on animals have demonstrated that the particulate phase of tobacco smoke contains certain chemical compounds which can act as complete carcinogens, tumor initiators, or tumor promoters. Recently, other compounds have been described that have no independent activity in two-stage carcinogenesis but *accelerate* the carcinogenic effects of polynuclear aromatic hydrocarbons in the initiator-promoter system.
5. Additional epidemiological evidence confirms a significant association between the combined use of cigarettes and alcohol, and cancer of the esophagus.
6. Epidemiological studies have demonstrated a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the risk of developing bladder cancer increases with inhalation and the number of cigarettes smoked.
7. Epidemiological evidence demonstrates a significant association between cigarette smoking and cancer of the pancreas.

SUMMARY: PREGNANCY

Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birth weight and an increased incidence of prematurity, defined by weight. There is increasing evidence to support the view that women who smoke during pregnancy have a significantly greater risk of an unsuccessful pregnancy than those who do not.

SUMMARY: GASTROINTESTINAL DISORDERS

Cigarette smoking males have an increased prevalence of peptic ulcer disease as compared to nonsmoking males and a greater peptic ulcer mortality ratio. These relationships are stronger for gastric ulcer than for duodenal ulcer. Smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of ulcer healing.

Highlights of the 1972 Report: Gastrointestinal Disorders

1. A possible link between cigarette smoking and peptic ulcer has been demonstrated in dogs in which nicotine was found to inhibit pancreatic and hepatic bicarbonate secretion. This could lead to peptic disease by depriving the duodenum of sufficient alkaline secretion to neutralize gastric acidity.
2. An investigation in human volunteers has suggested that cigarette smoking decreases the effectiveness of the lower-esophageal sphincter as a barrier against gastro-esophageal reflux.

SUMMARY: TOBACCO AMBLYOPIA*

Tobacco amblyopia is presently a rare disorder in the United States. The evidence suggests that this disorder is related to nutritional or idiopathic deficiencies in certain detoxification mechanisms, particularly in the metabolism of the cyanide component of tobacco smoke.

SUMMARY: NON-NEOPLASTIC ORAL DISEASE*

Ulceromembranous gingivitis, alveolar bone loss, and stomatitis nicotina are more commonly found among smokers than among nonsmokers. The influence of smoking on periodontal disease and gingivitis probably operates in conjunction with poor oral hygiene. In addition, there is evidence that smoking may be associated with edentulism and delayed socket healing. While further experimental and clinical studies are indicated, it would appear that nonsmokers have an advantage over smokers in terms of their oral health.

The information contained in the following three summary statements: Allergy, Public Exposure to Air Pollution from Tobacco Smoke, and Harmful Constituents of Cigarette Smoke, is new and appears for the first time.

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* This summary statement is the same as that appearing in previous reports, because new studies adding to the understanding of this area have not appeared. Consequently, the literature in this area is not reviewed and the statement is only included to complete this summary chapter.

SUMMARY OF THE 1972 REPORT: ALLERGY

1. Tobacco leaf, tobacco pollen, and tobacco smoke are antigenic in man and animals.
2. (a) Skin sensitizing antibodies specific for tobacco antigens have been found frequently in smokers and nonsmokers. They appear to occur more often in allergic individuals. Precipitating antibodies specific for tobacco antigens have also been found in both smokers and nonsmokers.
   (b) A delayed type of hypersensitivity to tobacco has been demonstrated in man.
   (c) Tobacco may exert an adverse effect on protective mechanisms of the immune system in man and animals.
3. (a) Tobacco smoke can contribute to the discomfort of many individuals. It exerts complex pharmacologic, irritative, and allergic effects, the clinical manifestations of which may be indistinguishable from one another.
   (b) Exposure to tobacco smoke may produce exacerbation of allergic symptoms in nonsmokers who are suffering from allergies of diverse causes.
4. Little is known about the pathogenesis of tobacco allergy and its possible relationship to other smoking-related diseases.

SUMMARY OF THE 1972 REPORT: PUBLIC EXPOSURE TO AIR POLLUTION FROM TOBACCO SMOKE

1. An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals.
2. The level of carbon monoxide attained in experiments using rooms filled with tobacco smoke has been shown to equal, and at times to exceed, the legal limits for maximum air pollution permitted for ambient air quality in several localities and can also exceed the occupational Threshold Limit Value for a normal work period presently in effect for the United States as a whole. The presence of such levels indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease and coronary heart disease.
3. Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various

concentrations to affect adversely animal pulmonary and cardiac structure and function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known.

SUMMARY OF THE 1972 REPORT: HARMFUL CONSTITUENTS OF CIGARETTE SMOKE

A number of substances or classes of substances found in cigarette smoke are identified as those which are judged to be contributors to the health hazards of smoking. These constituents are further divided into the *most likely* contributors to these health hazards (carbon monoxide, nicotine, and tobacco "tar"), substances which are *probable* contributors, and those which are *suspected* contributors. The recommendations for control in this area are to seek progressive reduction of all harmful constituents in cigarette smoke with priority being given first to the most likely contributors named and second to the probable contributors to the health hazards of smoking. These judgments represent the consensus of experts based on current knowledge and are subject to modification and further elaboration as more knowledge becomes available.

CHAPTER 2

Cardiovascular Diseases

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INTRODUCTION

In the United States more people die from coronary heart disease (CHD) than from any other disease; furthermore, CHD is the single most important cause of excess death among cigarette smokers (*54, 57*). The 1971 report, "The Health Consequences of Smoking" (*56*), outlined the growing magnitude of this problem and summarized the relationship between smoking and coronary heart disease as follows:

1. Data from numerous prospective and retrospective studies confirm the judgment that cigarette smoking is a significant risk factor contributing to the development of coronary heart disease including fatal CHD and its most severe expression, sudden and unexpected death. The risk of CHD incurred by smokers of pipes and cigars is appreciably less than that by cigarette smokers.
2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) shows that cigarette smoking operates independently of these other factors and can act jointly with certain of them to increase the risk of CHD appreciably.
3. There is evidence that cigarette smoking may accelerate the pathophysiological changes of pre-existing coronary heart disease and therefore contributes to sudden death from CHD.
4. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries.
5. The cessation of smoking is associated with a decreased risk of death from CHD.
6. Experimental studies in animals and humans suggest that cigarette smoking may contribute to the development of CHD and/or its manifestations by one or more of the following mechanisms:
   a. Cigarette smoking, by contributing to the release of catecholamines, causes increased myocardial wall tension, contraction velocity, and heart rate, and thereby increases the work of the heart and the myocardial demand for oxygen and other nutrients.

b. Among individuals with coronary atherosclerosis, cigarette smoking appears to create an imbalance between the increased needs of the myocardium and an insufficient increase in coronary blood flow and oxygenation.

c. Carboxyhemoglobin, formed from the inhaled carbon monoxide, diminishes the availability of oxygen to the myocardium and may also contribute to the development of atherosclerosis.

d. The impairment of pulmonary function caused by cigarette smoking may contribute to arterial hypoxemia, thus reducing the amount of oxygen available to the myocardium.

e. Cigarette smoking may cause an increase in platelet adhesiveness which might contribute to acute thrombus formation.

Recent epidemiological, pathological, and experimental studies add to the understanding of the relationship between smoking and CHD. These studies point to cigarette smoking as one of the major risk factors leading to CHD and help clarify some of the biomechanisms through which this occurs.

EPIDEMIOLOGICAL STUDIES

A prospective study of 973 men born in 1913 in Göteborg, Sweden, was undertaken in 1963 (*51, 52*). The proportion of myocardial infarctions among cigarette smokers was significantly greater than among nonsmokers ($P < .05$), and the incidence of myocardial infarction rose with increasing cigarette consumption (table 1). Of the 35 individuals who experienced a myocardial infarction between 1963 and 1970, only two had been nonsmokers; in the whole population of men born in 1913, 56 percent were smokers.

Although angina pectoris was more common in smokers than nonsmokers, the difference was smaller than for myocardial infarction and was not statistically significant (*52*).

Paffenbarger, et al. (*42*) reported on the health experience of 3,263 longshoremen studied over the past 18 years. During this interval 1,098 were known to have died, 350 dying from CHD. Longshoremen who smoked more than 20 cigarettes a day faced a risk of coronary death which was more than twice as great as that of the group made up of both nonsmokers and smokers of less than 20 cigarettes a day ($P < .01$).

Keys, et al. (*30*) analyzed the 20-year CHD incidence among 279 Minnesota men aged 47 through 57 years who were CHD free at entry into the study. The relationship of cigarette smoking habits at the start of the study to the subsequent incidence of CHD was examined. The originally published table of results was incorrect and the authors have supplied a corrected table which appeared in a later issue of the same journal (table 2). The morbidity ratio for "hard CHD" (CHD deaths plus myocardial infarctions not resulting in death) among those smoking more than 10 cigarettes a

TABLE 1.—*Incidence (1963–1970) of heart infarct in relation to tobacco consumption in "The Men Born in 1913," Göteborg, Sweden.*

n = 855

Smoking classification	Heart infarct Number	 Percent
Never smoked n = 207	(2)	1.0
Stopped smoking n = 168	(2)	1.0
Cigarette smokers 1–14 cig/day n = 234	(13)	6.0
15–24 cig/day n = 138	(9)	7.0
≧25 cig/day n = 33	(4)	12.0
Pipe/cigar n = 75	(5)	7.0

SOURCE: Tibblin, G., Wilhelmsen, L. (51).

TABLE 2.—*Cigarette smoking at entry and subsequent 20-year CHD incidence among Minnesota men.*[1]

Age	Number of men	Item	Never	Smoking habit (cigarettes/day) Stopped	 <10	 10-19	 >20
47, 48	53	% with habit	23	19	9	19	30
49, 50	51	% with habit	33	20	14	10	23
51, 52	69	% with habit	33	26	14	14	13
53, 54	53	% with habit	36	30	8	13	13
55–57	51	% with habit	24	33	8	18	17
47–57	277	Number of men	83	71	30	41	52
47–57	277	Hard CHD rate (%)	12.0	15.5	10.0	17.1	21.2
47–57	277	Hard CHD rate (SE)	± 3.6	+ 4.3	± 5.5	± 5.9	± 5.7
47–57	277	Hard CHD Morbidity Ratio	1.00	1.29	.83	1.43	1.77
47–57	277	All CHD rate (%)	±21.7	±21.1	±16.7	±19.5	±26.9
47–57	277	All CHD rate (SE)	± 4.5	± 4.8	± 6.8	± 6.2	± 6.1
47–57	277	All CHD Morbidity Ratio	1.00	.97	.77	.90	1.24

[1] Cigarette smoking habits, by age at start of the 20-year follow-up, 20-year incidence rates (per 100 men), and standard errors (SE) of the rates. "Hard CHD"—CHD death and myocardial infarcts. "All"—angina pectoris and other CHD diagnoses. "Deaths"—from all causes except violence.

SOURCE: Modified from Keys, A., et al. (30).

day is similar to that reported from the large prospective studies. However, with the small number of cases in each smoking category, there are no statistically significant differences in the incidence of CHD between the categories, either singly or combined.

Retrospective studies of CHD have recently been reported from Czechoslovakia, Sweden, Norway, and India which corroborate earlier studies linking cigarette smoking with excess CHD morbidity and mortality.

The Prague study (*19*) included 443 men between the ages of 60 and 64 years. Significantly more ($P < .05$) individuals with a "probable" myocardial infarction were found among cigarette smokers than among nonsmokers or pipe and cigar smokers.

The smoking habits of 120 patients with myocardial infarction who were hospitalized in Göteborg were compared with those of the entire "men born in 1913" population sample (*17, 62*). A significantly ($P < .01$) greater number of smokers and heavy smokers (more than 15 cigarettes a day) were found in the myocardial infarction group than in the population sample.

The Bergen, Norway, cross sectional study of 2,117 women and 2,472 men documented a relationship between smoking and CHD in men, which was most marked in the 50 to 59 year old age group (*16*). No effect of smoking on the prevalence of CHD in women was demonstrable in this study, and the effect in men did not appear to be related to the daily number of cigarettes smoked.

In New Delhi, 100 "well documented" cases of ischemic heart disease were compared with an equal number of control cases (*8*). In this study, significantly more ($P < .01$) of the case group smoked cigarettes regularly than the control group (Morbidity Ratio = 2.1).

Mulcahy, et al. (*40*) recently found a positive association between coronary heart disease mortality rate and calculated per capita cigarette consumption in 21 countries. He interpreted the results as being consistent with the hypothesis that cigarette smoking is a significant risk factor in CHD mortality.

Stamler, et al. (*50*) found that for both men and women the 1964 CHD mortality rates in 17 developed countries were related to average annual per capita cigarette consumption.

INTERACTION OF SMOKING AND OTHER RISK FACTORS

The Report of the Inter-Society Commission for Heart Disease Resources summarized the evidence indicating that three risk factors (hypercholesterolemia, hypertension, and cigarette smoking) are properly designated major risk factors for premature CHD (*28*). Other possible risk factors including obesity, physical inactivity, diabetes mellitus, elevated resting heart rate, electrocardiographic abnormalities, a positive family history of premature CHD, and psychologic and social factors have also been described (*54, 55, 56*).

In the study of 973 men born in 1913 in Göteborg, Sweden, several coronary risk factors including elevated serum cholesterol, elevated serum triglyceride, low physical activity at work, and smoking were found to be related to an increased risk for the development of coronary heart disease during the subsequent years of the study. Failure to find a relationship between hypertension and an increased risk of CHD may have been due to the fact that all patients with hypertension in 1963 have been under treatment since that time.

Tibblin and Wilhelmsen (*52*) found that as a patient accumulated more risk factors his chance of developing CHD became substantially greater. Werkö (*61*) reported from the same Göteborg study that patients who were smokers, had sedentary jobs, and had both elevated cholesterol and triglycerides experienced a 4-year incidence of new coronary events of about 20 percent; the 4-year incidence among those who exhibited only one or two risk factors was much lower, ranging from 0 to 3 percent. ECG changes and anginal pain were included in the definition of new coronary events.

Paffenbarger, et al. (*42*) evaluated coronary risk factors in the study of 3,263 longshoremen. They found that, with the exception of diagnosed heart disease, smoking was the most important factor predictive of high risk for coronary mortality.

Keys, et al. (*30*) in the study of 279 Minnesota men, concluded that a positive cold pressor test, elevated serum cholesterol, and elevated systolic blood pressure had major predictive power for CHD death or infarction; in their analysis smoking seemed less important.

Stamler (*49*) has analyzed the data on 13 deaths occurring during the first years of the Chicago Coronary Prevention Evaluation Program, which originally consisted of 519 coronary-prone male volunteers aged 40 to 59 who were free from clinical CHD. Eleven of the 13 decedents had three or more coronary risk factors at entry into the program, and at least 8 were cigarette smokers at the time of death. Forty-three men, who were cigarette smokers at entry into the Coronary Prevention Evaluation Program, gave up smoking and have remained active in the program. There have been no deaths from cardiovascular causes in this group. Stamler (*49*) commented: "Even though the number of decedents was small, these data strongly suggest that continued cigarette smoking is associated with very high risk of premature death for very coronary-prone men, and that other preventive measures are by themselves of limited value for them as long as they fail to give up cigarette smoking."

As described in the 1971 report, "The Health Consequences of Smoking" (*56*), some studies have indicated that smokers show increased levels of serum lipids while others have not. Such contradictory results are also present in recent studies from Germany, Poland, and Sweden (*21, 39, 53*).

After a patient suffers a myocardial infarction, he frequently gives up smoking (*17, 26*). Only fragmentary data are available on what effect the cessation of cigarette smoking might have on the likelihood of a recurrent myocardial infarction (*9, 34, 43*). Ninety-two survivors of a first myocardial infarction were studied over a 3-year period by Parás Chavero, et al. (*43*). During this time, 37 patients continued smoking, and 12 of them (32 percent) experienced a second myocardial infarction. The 51 patients who did not smoke during this 3-year period included 39 ex-smokers and 12 patients who had never smoked. Eight of the nonsmokers (16 percent) experienced a second myocardial infarction. The smoking habits of four of the patients were not known. Although the continuing smokers experienced a greater rate of recurrent myocardial infarction than the nonsmokers, the difference was not statistically significant (P = .07).

The role of genetic factors in the development of CHD and the difficulties associated with the use of twin studies were discussed in the 1971 report, "The Health Consequences of Smoking" (*56*). Mailed questionnaires were used to establish the diagnosis of angina pectoris in a study by Lundman, et al. of twin pairs discordant with respect to smoking habits and in a study by Liljefors of twins with CHD. Lundman, et al. (*36*) recently investigated 69 male twins with the diagnosis of angina pectoris established by questionnaire. Only 22 percent of these diagnoses could be verified by clinical examination.

In a study of CHD, Liljefors (*35*) studied 91 pairs of twins from the Swedish Twin Registry of 1967. The twins ranged in age from 42 to 67 years, and 51 pairs were monozygotic. Smoking habits were not significantly different in pairs discordant for the probable presence of CHD. However, Liljefors noted that "... in many pairs the smoking habits were similar and that the material included few pairs discordant with respect to smoking, so that it does not provide a suitable basis for conclusions as to the causal importance of smoking for CHD." As observed in the 1971 report, "The Health Consequences of Smoking" (*56*), it would be surprising if genetic factors did not play a role in heart disease; however, it is open to question whether findings from twin studies can be used to distinguish between "... the hypothesis that genetic factors govern the level of host susceptibility or resistance to the effects of an exogenous influence such as cigarette smoking and the hypothesis that genetic factors 'cause' both heart disease and smoking."

AUTOPSY STUDIES

In previously reported autopsy studies, Auerbach, et al. found that aortic and coronary atherosclerosis in man were more common and severe among smokers than among nonsmokers (*5*). They have now extended their investigations to the myocardial arterioles of men and beagle dogs (*6*). In a study of 1,184 men, they found that the thickness of myocardial arteriole walls was greater, on the average, in smokers than nonsmokers (table 3). The thickness increased with the number of cigarettes smoked per day and with age. The thickness was less, on the average, among cigar and pipe smokers than among cigarette smokers, but it was greater than in men who had never smoked regularly.

TABLE 3.—*Human autopsy study. Comparison of the thickness of myocardial arteriole walls in smokers and nonsmokers.*[1]

Age (year)	Smoking	Total	Number of Men 0	‡Grade 1	‡Grade 2, 3	‡Grade Total	Percent of Men ‡Grade 0	‡Grade 1	‡Grade 2,3
< 45	None	22	2	19	1	100.0	9.1	85.4	4.5
	Cigar, pipe	4	—	1	3	100.0	—	†25.0	†75.0
	Cig. 1–19	50	1	31	18	100.0	2.0	62.0	36.0
	Cig. 20–39	85	4	35	46	100.0	4.7	41.2	54.1
	Cig. ≧40	29	—	10	19	100.0	—	34.5	65.5
45–59	None	15	1	12	2	100.0	6.7	80.0	13.3
	Cigar, pipe	13	—	8	5	100.0	—	61.5	38.5
	Cig. 1–19	33	—	17	16	100.0	—	51.5	48.5
	Cig. 20–39	99	—	35	64	100.0	—	35.4	64.6
	Cig. ≧40	50	—	11	39	100.0	—	22.0	78.0
60–69	None	56	4	36	16	100.0	7.1	64.3	28.6
	Cigar, pipe	35	—	22	13	100.0	—	62.9	37.1
	Cig. 1–19	92	—	44	48	100.0	—	47.8	52.2
	Cig. 20–39	193	—	58	135	100.0	—	30.1	69.9
	Cig. ≧40	87	—	21	66	100.0	—	24.1	75.9
≧ 70	None	32	2	18	12	100.0	6.3	56.2	37.5
	Cigar, pipe	40	—	19	21	100.0	—	47.5	52.5
	Cig. 1–19	30	—	12	18	100.0	—	40.0	60.0
	Cig. 20–39	46	—	12	34	100.0	—	26.1	73.9
	Cig. ≧40	9	—	3	6	100.0	—	†33.3	†66.7

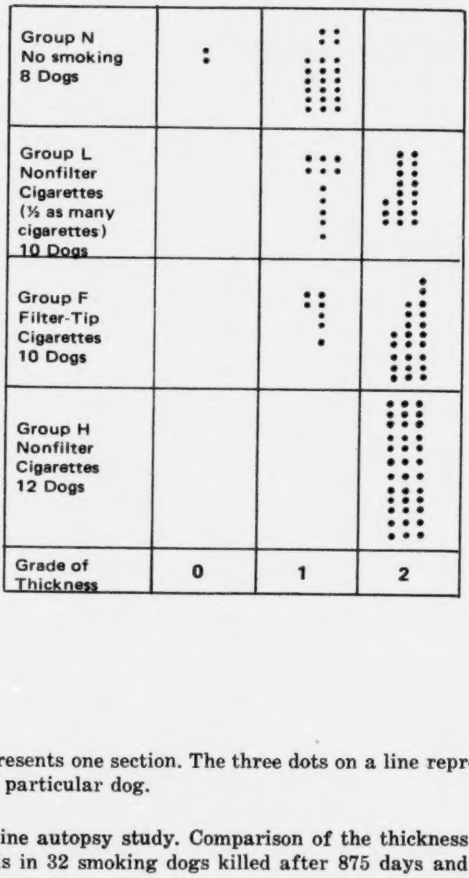
[1] In the right ventricular wall of 1,020 men by age and smoking habits.

† Percentages based on less than ten cases.

‡ Four Point Scale for the Thickness of Myocardial Arteriole Walls:
0—normal thickness; 1—slight thickness; 2—moderate thickness; 3—great thickness.

SOURCE: Auerbach, O., et al. (6).

In one experiment, beagle dogs inhaled cigarette smoke daily through tracheostomae. Twenty-eight dogs that died between days 57 and 875 formed one group; 32 dogs that were killed after 875 days formed another group. Eight control dogs were not exposed. Beagle myocardial arteriole walls were found to be thicker in smoking than nonsmoking dogs, in dogs smoking many cigarettes than in dogs smoking fewer cigarettes, and in dogs smoking nonfilter cigarettes than in dogs smoking filter-tip cigarettes (figure 1). Also, the thickness of arteriole walls increased with the duration of smoking.



Each dot represents one section. The three dots on a line represent the three sections from a particular dog.

FIGURE 1.—Canine autopsy study. Comparison of the thickness of myocardial arteriole walls in 32 smoking dogs killed after 875 days and 8 nonsmoking dogs.

SOURCE: Auerbach, O., et al. (6).

EXPERIMENTAL STUDIES

NICOTINE AND CIGARETTE SMOKE

Schievelbein, et al. (*47*) investigated the effect of oral nicotine administration over a 20-month period on lipid metabolism in 35 rabbits. Even though lipoprotein lipase levels and calcium content of the aorta were significantly greater in the group given nicotine than in the control group, the histological changes of arteriosclerosis were found with equal frequency in both groups. The authors concluded that the epidemiological correlations between CHD and cigarette smoking could not be explained by the pharmacologic effect of nicotine alone.

A study of the interaction of chronic nicotine administration and acute hypoxia in 280 rats was performed by Wenzel and Richards (*60*). Pretreatment of the rats with nicotine increased the mortality during hypoxia, but the difference was not statistically significant. Pretreatment with the nicotine also was associated with marked variability of regression of hypoxic heart lesions. The interaction of nicotine pretreatment and the hypoxic insult produced variable effects on myocardial enzymes.

Aronow (*1*) recently studied the effect of cigarette smoking on the A wave of the apexcardiogram in 20 men with CHD. The A wave reflects the left ventricular filling wave associated with the impact of blood upon the ventricular wall during left atrial contraction. He found that the mean maximum increase in A wave ratio after smoking was 34 percent for high-nicotine cigarettes, 13 percent for the low-nicotine cigarettes, and 6 percent for the non-nicotine cigarettes. He ascribed these changes to increased myocardial ischemia produced by cigarette smoking, which was reflected by a larger A wave ratio in the apexcardiogram. While nicotine appears to have produced most of these changes, the observation that a 6 percent increase occurred in the absence of nicotine suggests the possibility that carbon monoxide plays a role in this effect.

CARBON MONOXIDE

Because cigarette smoke contains from 2.7 to 6 percent carbon monoxide (CO), significantly higher carboxyhemoglobin (COHb) levels are found in smokers than nonsmokers (*13, 20, 24, 63*). COHb levels in nonsmokers are usually less than 1 percent, while those in smokers average around 4 percent and may exceed 15 percent (*4, 20, 56*). Heavy smokers and those who inhale show the highest carboxyhemoglobin levels (*20*).

Haebisch (*24*) found that a smoker with a daily consumption of 35 to 40 cigarettes easily attains and maintains for hours an alveolar

CO concentration of 50 p.p.m., which reaches or exceeds legally-established ambient air quality standards (*14, 18, 23, 24*).

Cohen, et al. (*13*) and Aronow, et al. (*2*) have shown that there is no significant difference in mean expired air carbon monoxide levels after patients have smoked tobacco or lettuce leaf cigarettes. Although pipe and cigar smokers in the United States are reported to have lower exposure to CO than cigarette smokers (*20*), CO intoxication has been reported in cigar smokers (*25*).

CO exerts its adverse effects on the cardiovascular system of smokers through one or more of the following mechanisms: (a) reduction of the amount of hemoglobin available for oxygen transport; (b) shift of the oxygen-hemoglobin dissociation curve to the left with consequent interference in oxygen release at the tissue level; and (c) induction of arterial hypoxemia. CO may interfere with the homeostatic mechanism by which 2,3-DPG controls the affinity of hemoglobin for oxygen (*56*). CO has also been implicated in experimental atherogenesis in animals (*56*).

Ayres, et al. (*7*) recently studied 41 patients during diagnostic cardiac catheterization, at which time they inhaled either 5 percent or .1 percent CO. Arterial and mixed venous oxygen tensions were decreased by administration of either concentration. In patients with CHD, coronary artery O_2 extraction decreased 7.9 percent after inhalation of .1 percent CO and 30.5 percent after inhalation of 5 percent CO. Some of the patients with CHD experienced changes in lactate and pyruvate metabolism indicative of inadequate myocardial oxygenation. The higher level of CO inhalation in this experiment is comparable to that experienced intermittently by cigarette smokers.

Brewer and his colleagues (*11*) investigated cigarette smoking as a cause of hypoxemia in residents of Leadville, Colorado, at an altitude of 3,100 meters. The arterial pO_2 of 8 smokers was significantly lower ($P < .05$) than that of 12 nonsmokers, but this was reversible upon cessation of smoking. They concluded that the adverse effect of cigarette smoking on O_2 transport may be especially pronounced at high altitude and may restrict an individual's ability to adapt to reduced O_2 tensions (*11, 12*).

Kjeldsen (*31, 32*) examined 993 industrial workers, about one-half of whom were tobacco workers. Fifty-nine cases of arteriosclerosis were documented by such clinical symptoms as angina pectoris and intermittent claudication or by a previous history of myocardial infarction. While 20.9 percent of the 934 "control" individuals were nonsmokers, only 2 (3.4 percent) of the 59 patients with arteriosclerosis were nonsmokers. A significantly higher percentage of diseased workers were heavy smokers and inhaled the smoke.

The diseased smokers had significantly higher carboxyhemoglobin and serum cholesterol levels than either smoking or nonsmoking control patients. This was true after standardizing for differences in levels of smoking between controls and diseased patients. As expected, there was a gradient in carboxyhemoglobin levels from lower levels in light smokers to higher levels in heavy smokers (table 4).

TABLE 4.—*Average values of carboxyhemoglobin and serum cholesterol in Danish smokers and nonsmokers in control group and group of patients with arteriosclerotic cardiovascular disease.*

Smoking category	Carboxyhemoglobin (saturation percentage) controls M±S.D.	patients M±S.D.	significance	Serum cholesterol (mg/100 ml) controls M±S.D.	patients M±S.D.	significance
Smokers	4.2±3.1 (738)[a]	7.0±3.7 (57)	$p<0.001$ $t=5.52$	247±44 (738)	290±33 (57)	$p<0.001$ $t=4.89$
Nonsmokers	0.4±0.9 (196)	0.5±0.7 (2)	n.s. $t=0.16$	236±49 (196)	284±56 (2)	$p<0.02$ $t=2.32$
Light smokers	2.5±2.5 (121)	3.7±2.5 (3)	n.s. $t=0.76$	245±38 (121)	279±67 (3)	n.s. $t=1.45$
Moderate smokers	4.1±3.0 (463)	7.3±3.6 (34)	$p<0.001$ $t=4.95$	246±45 (463)	286±50 (34)	$p<0.001$ $t=4.52$
Heavy smokers	5.7±3.0 (154)	7.0±4.0 (20)	n.s. $t=1.45$	253±45 (154)	298±53 (20)	$p<0.05$ $t=2.18$

p = Probability that difference is not due to chance.
t = Student's t calculation.
n.s. = not significant.
[a] The number of subjects in each category is enclosed in parentheses beneath the mean (M) and standard deviation (S.D.).

SOURCE: Kjeldsen, K. (31).

Kjeldsen also observed that the COHb levels of 8 to 19 percent seen in 40 percent of the patients with arteriosclerosis were of the same magnitude as those provoking experimental atherosclerosis and cardiac necrosis in animals.

SMOKING AND THROMBOSIS

Previous reports of the Surgeon General on smoking and health have reviewed the effects of smoking on thrombus formation (*54, 55, 56*). The role of thrombosis in CHD remains an active area of investigation. Recent studies have not thus far yielded a unifying concept of the effect of smoking on thrombosis (*33, 41, 48*).

CHOLESTEROL CONTENT OF TOBACCO AND TOBACCO SMOKE

Cholesterol glucoside has not previously been reported in tobacco, or in any other plant (*10*). Bolt and Clarke (*10*) investigated the sterolin and sterol fraction of flue-cured tobacco and found that cholesterol is one of the major components of the sterol fraction.

More recently, Grunwald, et al. (*22*) have confirmed that cholesterol accounts for 10 percent of the total sterol in cigarette tobacco. They also found that 8.6 percent of the total sterol content of cigarette smoke condensate was cholesterol. Thirteen percent of the cholesterol present in cigarette tobacco was transferred to the condensate.

The biological significance of these findings remains to be determined.

COR PULMONALE (PULMONARY HEART DISEASE)

The relationship between cigarette smoking and chronic obstructive bronchopulmonary disease (COPD) with cor pulmonale was discussed in the 1968 Supplement to "The Health Consequences of Smoking" (*55*).

Although the extent of morbidity and mortality due to cor pulmonale and right heart failure is difficult to determine, COPD is often complicated by these conditions (*27*).

The Pulmonary Heart Disease Study Group of the Inter-Society Commission for Heart Disease Resources recently summarized the evidence linking cigarette smoking with COPD and concluded: "Cigarette smoking is the major cause of pulmonary heart disease in that it is the most important cause of the chronic non-neoplastic bronchopulmonary diseases in the United States" (*28*).

CEREBROVASCULAR DISEASE

The 1971 report, "The Health Consequences of Smoking" (*56*), summarized the data linking smoking to cerebrovascular disease as follows:

1. Data from numerous prospective studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease.
2. Experimental evidence concerning the relationship of smoking and cerebrovascular disease is at present insufficient to allow for conclusions concerning pathogenesis. However, some of the pathophysiological considerations discussed concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

In the interim, additional reports have been published.

Dyken (*15*) performed a retrospective study on 285 patients with cerebrovascular disease in Elkhart, Indiana. Even though low cigarette consumption was noted in all groups, males who had cerebral infarctions smoked significantly more than controls.

Paffenbarger, et al. (*42*) found that smokers of more than 20 cigarettes a day faced a slightly increased but not significantly greater risk of dying from a stroke than those smoking lesser amounts.

After 16 years follow-up, male cigarette smokers in the Framingham study had more than three times the nonsmokers' risk of developing a cerebral infarction (*29*). However, Kannel commented: "It is not clear that smoking actually affects the rate of cerebral atherogenesis, and some other mechanism may be involved."

PERIPHERAL VASCULAR DISEASE

The 1971 report, "The Health Consequences of Smoking" (*56*), summarized the data relating smoking to peripheral vascular disease as follows:

1. Data from a number of retrospective studies have indicated that cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking also appears to be a factor in the aggravation of peripheral vascular disease.
2. Cigarette smoking has been observed to alter peripheral blood flow and peripheral vascular resistance.

Newly published studies add to our understanding of the effect of nicotine or tobacco smoke on the peripheral circulation and of the significance of smoking in peripheral vessel atherogenesis.

Martz, et al. (*37*) observed that some of the apparently conflicting data on the effects of nicotine upon the peripheral vasculature may result from interpretations based upon indirect measurements of microcirculatory variables. Hence, they studied vascular changes in a bat wing under direct microscopic observation. They noted a marked increase in the diameter of innervated, minute arteries with intraperitoneal nicotine administration, but this effect was abolished with sympathetic denervation.

Asano and Branemark (*3*) installed a direct, microscopic observation chamber in the connective tissue of two human volunteers. One volunteer was a "healthy" 20-year-old male nonsmoker. The other volunteer was a diabetic who had been a smoker for five years and who "... had no apparent diabetic vasculopathy." The effects of tobacco smoking on the microcirculation of these volunteers included: "... vasoconstriction, decrease in blood flow rate and frequency of plasma spacing, blocking of blood flow in varying numbers of nutritive capillaries, shunting of blood from arterioles to venules. . . ." These microcirculatory changes were said to result in a decrease of nutritive blood flow in tissue.

As mentioned in the discussion of CHD, Kjeldsen (*31, 32*) studied several smoking patients with occlusive peripheral vascular disease whose COHb levels were significantly higher than those of control smokers. The levels of COHb in many of these patients were comparable to those associated with experimental atherosclerosis in animals. Astrup, et al. (*4*) have suggested that prospective studies should be performed to investigate the relationship between COHb levels and the incidence of arterial disease.

In the Prague study (*19*) intermittent claudication was significantly ($P < .01$) more common among cigarette smokers than nonsmokers. Twenty percent of the men in the age group of 60 to 64 who were heavy smokers (more than 25 cigarettes a day) had intermittent claudication.

Räf (*44*) reported that all but 4 of the 98 patients admitted for peripheral vascular surgery at the Karoline Hospital, Sweden, were smokers.

Mathiesen, et al. (*38*) in Denmark followed the spontaneous course of arterial insufficiency in 211 patients. Cessation of smoking increased the number of patients displaying spontaneous improvement.

ORAL CONTRACEPTIVES, THROMBOPHLEBITIS, AND SMOKING

In two studies from Great Britain and one from the United States, it was reported that the use of oral contraceptives was associated with a significantly increased risk of developing venous thromboembolism (*46, 58, 59*). The British investigators also noted in their initial report that the affected patients were, on the average, heavier smokers than controls (*58*). However, after an additional year of study, a similar effect was not noted and they concluded (*59*) : "... the earlier difference between the smoking habits of the two groups can thus reasonably be attributed to chance ($P = 0.08$)." The American investigator (*45*) found "... no evidence that smoking, acting either independently or in conjunction with oral contraceptives, is a factor in idiopathic thromboembolism."

Cigarette smoking has not been clearly demonstrated to be a factor that contributes to the risk of idiopathic thromboembolism associated with the use of oral contraceptives. Nevertheless, the possibility that it may act to increase that risk has not yet been completely ruled out.

HIGHLIGHTS OF CURRENT CARDIOVASCULAR INFORMATION

In addition to the comprehensive summary from the 1971 report, "The Health Consequences of Smoking" (*56*), cited earlier in this chapter, the following statements are made to emphasize the most recent developments in the field:

1. Recent epidemiological studies from several countries confirm that cigarette smoking is one of the major risk factors contributing to the development of CHD. Avoidance of cigarette smoking is of importance in the primary prevention of CHD.
2. Studies in man and animals have shown a greater myocardial arteriole wall thickness in smokers than nonsmokers.
3. Experimental and epidemiological investigations implicate the elevation of carboxyhemoglobin levels in smokers as a contributor to the development of CHD and arteriosclerotic peripheral vascular disease.
4. Cigarette smoking is considered to be the major cause of pulmonary heart disease (cor pulmonale) in the United States in that it is the most important cause of chronic nonneoplastic bronchopulmonary diseases. Avoidance of cigarette smoking is of importance in the primary prevention of pulmonary heart disease.

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CHAPTER 3

Non-neoplastic Bronchopulmonary Diseases

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INTRODUCTION

Chronic bronchitis and emphysema are the chronic bronchopulmonary diseases of greatest health importance in the United States (*71*). The 1971 report, "The Health Consequences of Smoking" (*70*), summarized the relationship between smoking and these diseases as follows:

1. Cigarette smoking is the most important cause of chronic obstructive bronchopulmonary disease in the United States. Cigarette smoking increases the risk of dying from pulmonary emphysema and chronic bronchitis. Cigarette smokers show an increased prevalence of respiratory symptoms, including cough, sputum production, and breathlessness, when compared with nonsmokers. Ventilatory function is decreased in smokers when compared with nonsmokers.
2. Cigarette smoking does not appear to be related to death from bronchial asthma although it may increase the frequency and severity of asthmatic attacks in patients already suffering from this disease.
3. The risk of developing or dying from COPD among pipe and/or cigar smokers is probably higher than that among nonsmokers while clearly less than that among cigarette smokers.
4. Ex-cigarette smokers have lower death rates from COPD than do continuing smokers. The cessation of cigarette smoking is associated with improvement in ventilatory function and with a decrease in pulmonary symptom prevalence.
5. Young, relatively asymptomatic, cigarette smokers show measurably altered ventilatory function when compared with nonsmokers of the same age.
6. For the bulk of the population of the United States, the importance of cigarette smoking as a cause of COPD is much greater than that of atmospheric pollution or occupational exposure. However, exposure to excessive atmospheric pollution or dusty occupational materials, and cigarette smoking may act jointly to produce greater COPD morbidity and mortality.

7. The results of experiments in both animals and humans have demonstrated that the inhalation of cigarette smoke is associated with acute and chronic changes in ventilatory function and pulmonary histology. Cigarette smoking has been shown to alter the mechanism of pulmonary clearance and adversely affect ciliary function.
8. Pathological studies have shown that cigarette smokers who die of diseases other than COPD have histologic changes characteristic of COPD in the bronchial tree and pulmonary parenchyma more frequently than do nonsmokers.
9. Respiratory infections are more prevalent and severe among cigarette smokers, particularly heavy smokers, than among nonsmokers.
10. Cigarette smokers appear to develop postoperative pulmonary complications more frequently than nonsmokers.

Recent epidemiological, autopsy, and experimental studies confirm and extend the foregoing statements.

EPIDEMIOLOGICAL STUDIES

COPD MORTALITY

Over a period of 4 to 8 years, Burrows and Earle (*10*) studied 200 patients with symptomatic COPD whose mean FEV_1 was 1.0 ± 0.4 liter. Ninety-seven percent of these patients had a history of cigarette smoking; the average consumption for the entire group of 200 individuals was 23 cigarettes a day over a period of 41 years. Upon entry into the study, 59 percent were still regular smokers and 38 percent had discontinued smoking. Eighty-nine percent of the group were males and the mean age was 59.1 years.

A 47 percent 5-year mortality was observed in these 200 patients, and most deaths were "... directly attributable to the underlying lung disease or one of its complications." The relationship of continued smoking to the course of the disease was difficult to interpret. Patients who stopped smoking prior to entry into the study had a poorer survival than those who continued to use cigarettes. This was related to a tendency for patients to give up smoking when their illness was severe, and "... the apparent advantage of smokers was eliminated when patients with similar FEV_1 levels were compared." The authors reported no reduction of mortality in the group of patients who stopped smoking, even when smokers and ex-smokers with similar FEV_1 levels were compared.

Reduction of cigarette smoking was associated with a history of reduced expectoration, smaller measured sputum volume, and "... a favorable course of the vital capacity ($P < .01$)...."

The 1971 report, "The Health Consequences of Smoking" (*70*), included an analysis of the variety of ways in which smoking may be related to disease. COPD was cited as an example in which smoking probably initiates a disease process by producing progressive, irreversible damage. The 200 patients reported by Burrows and Earle (*10, 11*) may be representative of patients who have experienced progressive and irreversible pulmonary damage after many years of exposure to cigarette smoke. In such cases, "... cessation of smoking leaves impaired function which does not improve appreciably but does not continue to deteriorate from continued exposure to cigarette smoke. However, such function may deteriorate through aging or through exposure to other harmful agents" (*70*).

COPD MORBIDITY

New reports of chronic bronchopulmonary disease prevalence support the findings of earlier studies in which a greater prevalence was found among smokers than nonsmokers.

A repeat study of a Berlin, New Hampshire, population sample, which included more than 1,500 individuals, was carried out in 1967 by Ferris, et al. (*27*). In both this survey and the earlier 1961 survey, a greater prevalence of chronic nonspecific respiratory disease was found in cigarette smokers than nonsmokers.

The 1967 Berlin study demonstrated that cigarette smokers who inhaled deeply or moderately had generally higher prevalences of chronic nonspecific respiratory disease than those who did not inhale or inhaled only slightly.

After standardization for age, sex, and smoking habits, the prevalence of chronic nonspecific respiratory disease in the 1967 survey sample was slightly lower than in 1961. This may be accounted for by a decrease in air pollution.

In a random sample of 609 residents of Glenwood Springs, Colorado, a high prevalence of chronic bronchitis was found to be strongly related to smoking, particularly of cigarettes, and this relationship was independent of age, sex, or history of dust exposure at work (*52*). Chronic airway obstruction was found to be predominantly a disease of elderly male smokers and increased in frequency with increasing age after 49 years.

The Tecumseh study is a well-known continuing epidemiologic investigation of the entire community of Tecumseh, Michigan. In this study the relationship of parental longevity to ventilatory function and prevalence of chronic nonspecific respiratory disease among sons was recently analyzed (*17*). Death before age 65 of either parent was related to low values of 1-second forced expiratory volume among the sons. Maternal death before age 65 was also associated with increased prevalence of chronic bronchitis and emphysema among sons. Some, but not all, of these relationships were accounted for by differences in smoking habits of the sons. The authors also concluded: "The evidence strongly suggests that constitutional factors are involved" (*17*).

A higher prevalence of chronic bronchitis was found among smokers than nonsmokers ($P < .01$) in a study of 710 Yugoslavian workers (*43*). There was a direct relationship between the lifetime number of cigarettes smoked and the presence of chronic bronchitis.

Several papers have been published recently comparing respiratory symptoms such as cough and sputum production among smokers and nonsmokers in different populations. Two of the new studies were prospective investigations (*15, 38*). In all instances, symptoms were more common among cigarette smokers than nonsmokers (*1, 6, 8, 15, 38, 52, 63, 75*). In the three studies which reported on pipe and cigar smokers, the frequency of respiratory symptoms in this group was, in general, intermediate between those of cigarette smokers and nonsmokers (*6, 15, 52*).

Results of studies of pulmonary function in representative samples of different populations (*6, 17, 38, 63*), surveys of employees (*15, 43, 57*), and normal volunteers (*75*) indicate that cigarette smokers have lower average pulmonary function than nonsmokers.

Pulmonary diffusing capacity was found by Van Ganse, et al. (*72*) to decrease in men and women with aging and with an increase in current or lifetime cigarette consumption.

In general, a dose-response relationship between cigarette consumption and the development of respiratory symptoms and/or impaired pulmonary function was found in both men and women; as cigarette consumption increased, these abnormalities were found more frequently (*6, 38, 52, 72, 75*).

Woolf and Suero (*75*) studied the respiratory effects of cigarette smoking in 298 normal women. The prevalence of cough, sputum production, wheezing, and shortness of breath increased progressively with increased cigarette smoking. The results of the following tests of pulmonary function were significantly lower in smokers than in nonsmokers: forced vital capacity, forced expiratory volume in one second, maximal mid-expiratory flow, arterialized capillary blood oxygen tension at rest, specific conductance, and pulmonary diffusing capacity and fractional uptake of carbon monoxide during exercise.

Seely, et al. (*63*) examined 365 high school students in the New Haven area. They found that students with 1 to 5 years' smoking experience had excessive cough, sputum production, and shortness of breath. These young smokers also had lower flow rates at mid-vital capacity and at lower lung volumes than nonsmoking students. The authors have raised the question of whether smoking by high school students may lead to developmental arrest of the lung. They feel that follow-up pulmonary function studies in adolescents who stop smoking will help clarify this question.

In a study of 556 high school students from Oklahoma City, Addington, et al. (*1*) reported that respiratory symptoms were significantly more frequent in smokers than nonsmokers, but no significant differences were noted in the FEV_1 and the mean vital capacity.

Snider, et al. (*65*) investigated 1,403 patients with documented pulmonary tuberculosis for the presence of obstructive pulmonary disease. Airway obstruction was found in 62 percent of white men, 37 percent of nonwhite men, 36 percent of white women, and 17 percent of nonwhite women. Sixty-eight percent of the patients were current smokers and 15 percent were ex-smokers. Heavy smoking had less effect on the presence of airway obstruction than advanced tuberculosis or older age. These data were interpreted as showing the predominant importance of tuberculosis as a factor leading to airway obstruction in tuberculous patients. However, the authors also concluded: "The present data suggest the possibility of an additive effect of smoking with tuberculosis in producing airway obstruction."

CESSATION OF SMOKING

The salutary effect of stopping cigarette smoking on COPD mortality and morbidity has been noted in previous reports of the Surgeon General (*69, 70*).

A recent statement from the "Pulmonary Heart Disease Study Group" of the Inter-Society Commission for Heart Disease Resources (*41*) also emphasized this point: "The overwhelming cause and effect relationship between smoking, bronchitis-emphysema and pulmonary heart disease is such that there is little doubt that a radical reduction or elimination of the cigarette habit would result in a greatly lowered incidence of the chronic respiratory diseases and cor pulmonale."

In recent studies, a decrease in the prevalence of respiratory symptoms among ex-cigarette smokers has been demonstrated (*10, 15, 75*). Higgins, et al. (*38*) interpreted data from 1957 and 1966 surveys of chronic respiratory disease in England as suggesting that the benefits of giving up smoking on respiratory symptoms are less in those who have smoked for many years than in those who have smoked for shorter periods.

Baker, et al. (*5*) undertook a therapeutic program for previously unrecognized mild to moderate cases of COPD. One hundred thirty-four men were included in this study. Eighty-five percent of these men were cigarette smokers, 11 percent were ex-smokers, and 4 percent were nonsmokers. At the 6-month follow-up, 61 subjects were still in the treatment program. Patients were encouraged to stop smoking, and at the 6-month follow-up 34 percent of the cigarette smokers had stopped smoking, while 34 percent decreased their cigarette consumption by at least half. At the follow-up evaluation, approximately two-thirds of those who either gave up smoking or decreased their cigarette consumption showed improvement in symptoms. Thirty percent of those whose smoking habits did not change showed improvement in symptoms. No significant differences were found in the pulmonary function studies at the follow-up evaluation. Alteration of smoking habits was the single factor most closely related to symptomatic improvement.

OCCUPATIONAL HAZARDS

As observed by Bouhuys and Peters (*7*), the relative contributions of cigarette smoking and industrial exposure to the loss of lung function may at times be difficult to determine.

Recent studies in wool, textile, grain elevator, shipyard, pulp mill, steel, and underground mining industries have documented a higher prevalence of chronic bronchitis among cigarette smokers than nonsmokers (*9, 13, 19, 20, 39, 42, 47, 50*). Similar studies in steel, pulp mill, machine shop, and welding industries indicate a greater frequency of respiratory symptoms and/or diminished pulmonary function in smokers than in nonsmokers (*22, 23, 30, 39*).

Japanese investigators recently reported that former employees of a poison gas factory had a high prevalence of chronic bronchitis and expiratory slowing; a history of chronic bronchitis was obtained from 67 percent of smoking men and 47 percent of nonsmoking men who had manufactured mustard gas or lewisite (*54*).

In recent months several articles have been published on coal workers' pneumoconiosis. Because coal miners are not allowed to smoke at work, they must smoke their cigarettes during a shorter period of time than non-miners; nevertheless, the average coal miner smokes as many cigarettes a day as does the non-miner (*51*). Thus, his exposure tends to be more intense during the period in which he is smoking. Also, the documented hazard of chronic exposure to coal dust may be compounded by the deleterious effect of smoking on ciliary function.

Ashford, et al. (*4*) studied approximately 30,000 working coal miners in Great Britain. Their data suggest that smoking and pneumoconiosis act independently in the production of pulmonary symptoms.

A total of 801 working, anthracite coal miners from Pennsylvania were investigated by Tokuhata, et al. (*68*). Twenty-four percent of the smoking miners had pulmonary function impairment as compared with 11 percent of miners who did not smoke. Because the smokers developed their pulmonary function abnormalities after a much shorter underground work exposure, the authors suggested that smoking may significantly accelerate the development of pneumoconiosis among coal miners.

Rasmussen and Nelson (*61*) studied 368 soft-coal miners from the Southern Appalachian coal fields. All workers included in the study had been involved in the coal industry for at least five years. Miners with a smoking history of 30 pack-years or more showed a significant ($P < .01$) reduction of FEV_1 when compared to nonsmoking miners. Impairment of oxygen transfer was greater in both the 15 to 29.9 pack-year group and the 30 plus pack-year group than among the lifelong nonsmokers ($P < .01$).

One hundred sixty-two dyspneic soft-coal miners, who gave histories of lifelong abstinence from cigarette smoking, were examined by Rasmussen (*60*). Of these patients, 85.6 percent had some X-ray evidence of pneumoconiosis. The group as a whole was "... not representative of all coal miners, nor of all symptomatic coal miners." Even though 56 percent of these miners had "normal" ventilatory capacities, i.e., an FEV_1 which was 75 percent or greater of the predicted normal vital capacity, more than 90 percent had an alveolar-arterial oxygen gradient during exercise which exceeded 19.9 mmHg. In more than 95 percent of the "normal" group, this gradient was not associated with significant arterial oxygen desaturation during exercise. The loss of pulmonary function in the entire group of non-cigarette smokers was somewhat less than that found in a group of miners composed of cigarette smokers and nonsmokers; nonetheless, these findings demonstrate that, in the absence of cigarette smoking, coal dust exposure may be associated with abnormalities in oxygen transfer during exercise, despite the presence of a normal FEV_1.

An autopsy study of 144 Appalachian coal miners was carried out by Naeye, et al. (*53*). Several parameters of cardiac and pulmonary structure were examined with regard to the effect of smoking. The volume of pulmonary macules and nodules containing coal dust and the concentration of silica crystals and collagen in these macules and nodules were unrelated to smoking. Right ventricular hypertrophy, defined according to an index developed by Naeye, was present in all groups of miners but was more severe in the bituminous workers who smoked cigarettes. The emphysema index, which is a measurement of the percent of lung tissue comprised of abnormal air space, was determined only in bituminous coal miners. It was significantly greater in cigarette smokers than in nonsmokers. Goblet cell hyperplasia, which appeared to be present in the entire group, was somewhat greater in the bituminous coal miners who smoked than in the nonsmokers, but the differences were not statistically significant.

Several investigators have concluded that cigarette smoking by itself is more important in the production of respiratory disease, other than pneumoconiosis, among coal miners than is exposure to coal dust (*24, 34, 58, 68*). Rasmussen questions this view (*60*). There is no consensus in recent publications on what role cigarette smoke may play in the development of coal workers' pneumoconiosis (*24, 51, 53, 58, 68*).

Weiss (*73*) examined 100 asbestos textile workers and found a greater prevalence of pulmonary fibrosis among cigarette smokers than nonsmokers. The prevalence increased with increasing amount and duration of cigarette smoking and with increasing duration of exposure to asbestos.

GENETIC FACTORS

An infrequent genetic error, homozygous alpha$_1$-antitrypsin deficiency, has been commonly associated with the premature development of severe, panacinar emphysema. It is postulated that alpha$_1$-antitrypsin is essential to protect the lung against the destructive action of naturally occurring proteinases (*36*).

Related questions of current interest deal with the prevalence and significance of the heterozygous deficiency state (intermediate serum antitrypsin deficiency) and the interaction of smoking with the severe and intermediate deficiency states. Mittman, et al. (*49*) recently reviewed the limited data available on the smoking habits of patients with alpha$_1$-antitrypsin deficiency; the cigarette smoke exposure of patients with the intermediate deficiency appears to be greater than that of patients with the severe deficiency.

Cigarette smoking has been reported to be a possible precipitating factor in the development of COPD in the homozygous deficiency state (*40*). Some studies (*26, 44, 49, 67*) have demonstrated an association between the heterozygous deficiency state and the development of COPD, while other studies have not (*35,62*). Mittman, et al. (*49*) have suggested that the intermediate deficiency may predispose to lung disease by accentuating an individual's susceptibility to the harmful effects of external irritants. Whether or not cigarette smoking acts together with the homozygous or heterozygous deficiency states to increase the risk of developing either panacinar emphysema or the more common forms of COPD has not been adequately studied.

PATHOLOGICAL STUDIES

In previous investigations, a correlation has been found between cigarette smoking and the histologic changes characteristic of bronchitis and emphysema (*70*).

An autopsy study of 60 patients with COPD was performed by Cullen, et al. (*16*). Although they did not find a correlation between the smoking history, total emphysema score, type of emphysema, or bronchial histologic features, the authors noted that only three patients were non-cigarette smokers. These three patients were pipe or cigar smokers. Eight patients who had stopped smoking three years before death had the same bronchial histologic abnormalities as those who continued smoking until death. This suggests that the bronchial abnormalities had become irreversible at the time of smoking cessation.

Dunnill and Ryder (*21*) carried out a quantitative study of the relationship between chronic bronchitis, emphysema, and smoking. The lungs of 353 patients were examined at autopsy, and a smoking history was available in 179 cases. A small but significant ($P < .005$) difference was found between smokers and nonsmokers in the percentage volume of bronchial mucous glands. Emphysema, mainly the centrilobular type, was found significantly ($P < .001$) more frequently in men and women smokers than nonsmokers, and it occurred at a much younger age in the smokers.

EXPERIMENTAL STUDIES

HUMAN STUDIES

Anderson (*3*) observed in a few patients with and without COPD that cigarette smoking can produce V/Q (ventilation/perfusion) changes resulting in a significant average drop in PaO_2 (partial pressure of oxygen in arterial blood).

Clarke, et al. (*14*) studied the bronchoconstrictor effect of plain and filtered cigarettes in 16 men. Filtration of either the particulate or vapor phase of the smoke had a similar effect in reducing the bronchoconstrictor response to cigarette smoke inhalation.

Using a reference cigarette developed by the University of Kentucky, Diamond, et al. (*18*) measured pulmonary expiratory resistance immediately after smoking. Heavy smokers, whose control resistance values were significantly higher than those of moderate or nonsmokers, had a decrease in resistance, while nonsmokers had an increase. Although selected ventilatory function tests did not change significantly after smoking, the author noted that the methods used in this study are probably not sensitive enough to measure constriction in peripheral airways, where smoking is thought to exert an adverse effect.

ANIMAL STUDIES

Frasca, et al. (*32*) made electron microscopic observations in areas of fibrosis and emphysema of the lungs of dogs, which had been subjected to experimental cigarette smoking as reported by Hammond, et al. (*37*). Details of the smoking procedure were reviewed in the 1971 report, "The Health Consequences of Smoking" (*70*). The major findings in the study of Frasca, et al. were: a complete loss or marked reduction in the number of alveolar septal capillaries, a marked thickening of the alveolar septa due to increased amounts of collagen, thickening of the pleural stroma due to large amounts of collagen, and the presence of increased numbers of macrophages in both the pleura and parenchyma. Many of these macrophages were filled with pleomorphic cytoplasmic inclusions. Crystalline-like structures were found in membrane-bound inclusions and ferritin-like particles occurred both in large membrane-bound aggregates and lying free in the cytoplasm.

Flint, et al. (*29*) reported a significant increase in the number of polymorphonuclear leukocytes recoverable from the lungs of guinea pigs following exposure of these animals to cigarette smoke. Because no changes in serum alpha$_1$-antitrypsin levels were found in this setting, the authors hypothesized that an imbalance may occur between proteolytic enzymes released by polymorphonuclear leukocytes and the inhibitors of these enzymes.

The stress effects of forced mouth-breathing and inhalation of cigarette smoke on lung mitochondrial phosphorylation were studied in the guinea pig by Kyle and Riesen (*45*). Mouth-breathing alone was associated with impaired efficiency of phosphorylation at two mitochondrial loci, while mouth-breathing guinea pigs exposed to cigarette smoke lost efficiency at only one of these sites.

Aviado and coworkers have studied the effects of hormones on the pulmonary response to cigarette smoke inhalation and intravenous nicotine injection. Subcutaneous progesterone administration, prior to nicotine or smoke exposure, reduced the bronchoconstrictor response in rats (*64*). A similar experiment involving pretreatment of dogs with glucocorticoids resulted in variable bronchoconstrictor responses after exposure to cigarette smoke (*12*).

Nitrogen dioxide (NO_2), a gas found in cigarette smoke and some industrially polluted air, can destroy cellular membranes and subcellular structures (*25*). Continuous administration of low concentrations of NO_2 in rats has produced an emphysema-like disease (*66*). Falk has suggested that NO_2 may ". . . carry a major responsibility for the high incidence of emphysema in cigarette smokers" (*25*).

Stephens, et al. (*66*) examined ultrastructural changes in pulmonary connective tissue of rats exposed to 2 to 20 p.p.m. of NO_2 for varying periods of time. In the absence of significant cell destruction, striking alterations in both collagen fibrils and basement membranes were found.

OVERALL CLEARANCE

Pavia, et al. (*55, 56*) examined the effect of cigarette smoking on the mucociliary mechanism of the human lung. A temporary slowing of mucociliary clearance was found in a group of 22 elderly smokers (*56*). Eight of these subjects had mild restrictive impairment and two had airway obstruction. When percentage clearance by elderly cigarette smokers and nonsmokers was compared, significant differences were not demonstrable (*55*). In the latter study, patients with functional evidence of lung disease were not included.

Deposition and clearance of inhaled 2μ particles of iron oxide labeled with ^{198}Au were studied in 19 young, normal subjects by Lourenço, et al. (*46*). While tracheobronchial clearance began immediately after inhalation in nonsmokers, it was delayed for periods of 1 to 4 hours after inhalation in smokers.

Frances, et al. (*31*) studied the effect of cigarette smoke on particle transport on donkey nasociliary mucosa. This mucosa was found to be much more resistant to the effects of cigarette smoke than that in the donkey tracheobronchial tree. More recently, Albert, et al. (*2*) published a report that in one of three donkeys tolerance to cigarette smoke had developed in the tracheobronchial mucosa.

Weissbecker, et al. (*74*) examined *in vivo* mucus flow rates in cats exposed to cigarette smoke gas phase of varied composition. Several compounds, e.g., isoprene and nitrogen dioxide, when added in combination to the gas phase, were effective in reducing the mucus flow, compared to the effect of the gas phase alone. Other compounds, e.g., CO, diminished the mucostatic effect of the gas phase. Compounds producing mucostasis were ineffective when added to cigarette smoke. These experiments indicate that effects observed from pure compounds cannot be used to predict the effect of cigarette smoke on mucus transport.

PHAGOCYTOSIS

The recent literature concerning the effect of tobacco smoke on macrophage function is reviewed in the chapter on allergy of this report.

Pratt, et al. (*59*) have extended their studies on the ultrastructure of human alveolar macrophages. Macrophages obtained from smokers tend to contain more heterogeneous inclusions than those from nonsmokers. Angular and needle-like structures were observed only in the inclusions of smokers. The authors concluded that these structures "... may represent undigested smoke products...."

In an investigation of early emphysema found in patients who were autopsied, McLaughlin and Tueller (*48*) found brownish, pigmented alveolar macrophages in the intact parenchyma adjacent to areas of emphysema. Such macrophages were not found in normal lungs, but were found in sputum specimens of "... apparently healthy cigarette smokers." In heavy smokers many of the macrophages also contained iron particles.

THE SURFACTANT SYSTEM

Giammona, et al. (*33*) measured the surface tension of lung extracts and bronchial washings of dogs following exposure to cigarette smoke. Elevated minimal surface tension values were found in bronchial washings obtained from three dogs. The values remained elevated for 48 hours after the cigarette smoke exposure; the values obtained one week after the cigarette smoke exposure were normal. The surface tension measurements of lung extracts obtained from four autopsied dogs were normal.

OTHER RESPIRATORY DISORDERS

Finklea, et al. (*28*) studied acute, noninfluenzal respiratory disease in military cadets and found significantly higher incidence rates for acute upper and lower respiratory illness among cigarette smokers than nonsmokers. Intermediate rates were found for lighter cigarette smokers, cigar, pipe, and ex-smokers.

HIGHLIGHTS OF CURRENT BRONCHOPULMONARY INFORMATION

In addition to the comprehensive summary from the 1971 report, "The Health Consequences of Smoking" (*70*), cited earlier in this chapter, the following statements are made to emphasize the most recent developments in the field:

1. Recent epidemiological and clinical studies from several countries confirm that men and women cigarette smokers have an increased prevalence of respiratory symptoms and have diminished pulmonary function compared to nonsmokers.
2. Investigations of high school students have demonstrated that abnormal pulmonary function and pulmonary symptoms are more common in smokers than nonsmokers.

3. Recent occupational studies confirm that cigarette smoking is an important cause of COPD, acting both independently and in combination with occupational exposure.

4. Recent experimental studies confirm that cigarette smoking exerts an adverse effect on pulmonary clearance and macrophage function.

5. Pulmonary macrophages obtained from cigarette smokers exhibit characteristic morphologic differences when compared to those obtained from nonsmokers.

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CHAPTER 4

Cancer

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LUNG CANCER

Cigarette smoking has been established as the major cause of lung cancer. The 1971 report, "The Health Consequences of Smoking" (*39*), in summarizing this association, concluded:

1. Epidemiological evidence derived from a number of prospective and retrospective studies coupled with experimental and pathological evidence confirms the conclusion that cigarette smoking is the main cause of lung cancer in men. These studies reveal that the risk of developing lung cancer increases with the number of cigarettes smoked per day, the duration of smoking, and earlier initiation, and diminishes with cessation of smoking.
2. Cigarette smoking is a cause of lung cancer in women but accounts for a smaller proportion of the cases than in men. The mortality rates for women who smoke, although significantly higher than for female nonsmokers, are lower than for men who smoke. This difference may be at least partially attributed to difference in exposure: the use of fewer cigarettes per day, the use of filtered and low "tar" cigarettes, and lower levels of inhalation. Nevertheless, even when women are compared with men who apparently have similar levels of exposure to cigarette smoke, the mortality ratios appear to be lower in women.
3. The risk of developing lung cancer among pipe and/or cigar smokers is higher than for nonsmokers but significantly lower than for cigarette smokers.
4. The risk of developing lung cancer appears to be higher among smokers who smoke high "tar" cigarettes or smoke in such a manner as to produce higher levels of "tar" in the inhaled smoke.
5. Ex-cigarette smokers have significantly lower death rates for lung cancer than continuing smokers. There is evidence to support the view that cessation of smoking by large numbers of cigarette smokers would be followed by lower lung cancer death rates.

6. Increased death rates from lung cancer have been observed among urban populations when compared with populations from rural environments. The evidence concerning the role of air pollution in the etiology of lung cancer is presently inconclusive. Factors such as occupational and smoking habit differences may also contribute to the urban-rural difference observed. Detailed epidemiologic surveys have shown that the urban factor exerts a small influence compared to the overriding effect of cigarette smoking in the development of lung cancer.

7. Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with these exposures in the pathogenesis of lung cancer so as to produce very much higher lung cancer death rates in those cigarette smokers who are also exposed to such substances.

8. Experimental studies on animals utilizing skin painting, tracheal instillation or implantation, and inhalation of cigarette smoke or its component compounds, have confirmed the presence of complete carcinogens as well as tumor initiators and promoters in tobacco smoke. Lung cancer has been found in dogs exposed to the inhalation of cigarette smoke over a period of more than two years.

In the interim, additional epidemiological, pathological, and experimental studies have added to our understanding of these relationships.

EPIDEMIOLOGICAL STUDIES

The major prospective epidemiological studies to date, demonstrating associations between cigarette smoking and specific diseases, were conducted primarily in the United States, Canada, and Great Britain in Caucasian populations. A large, prospective study currently in progress in Japan adds to the weight of evidence supporting a causal relationship between cigarette smoking and lung cancer. It is the first large-scale prospective study to be conducted in a population characterized by genetic, dietary, behavioral, and cultural influences distinctively different from those in previously examined Western populations. The 3-year preliminary prospective data for lung cancer from this population of 265,118 adults in Japan (*10*) demonstrate overall effects and dose-response relationships similar to those observed in previous studies (figure 1).

The mortality ratio for male smokers of 1 to 9 cigarettes a day was 2.7 and rose to 24.8 for smokers of more than 2 packs a day. The mortality ratio was 6.9 for ex-smokers. Of the 122,261 men in the study, 74.3 percent were daily smokers, 3.4 percent were ex-smokers, and 19.1 percent nonsmokers. The percentage of males who were daily smokers decreased with advancing age.

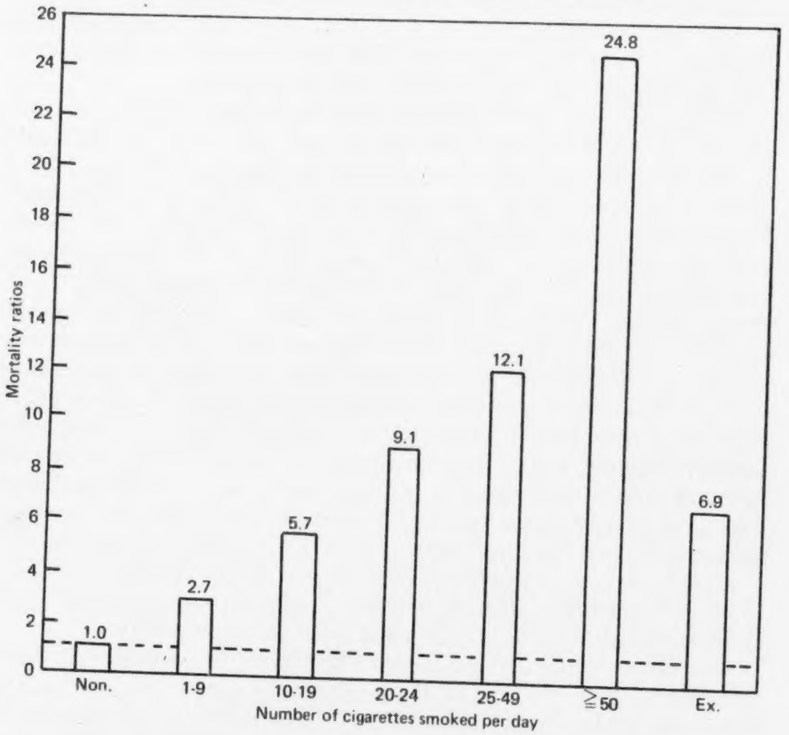


FIGURE 1.—Lung cancer mortality ratios of Japanese males by amount smoked.

SOURCE: Hirayama, T. (10).

In a prospective study of 12,322 Czechoslovakian males, Kubik, et al. (*19*) analyzed various factors associated with the development of lung cancer. During the 3½-year follow-up period, 61 cases of lung cancer were discovered. The incidence of lung cancer among males aged 40 to 64 was 460/100,000 among heavy cigarette smokers (more than 200,000 lifetime cigarettes), 90/100,000 for light cigarette smokers (less than 200,000 lifetime cigarettes), and 10/100,000 for nonsmokers. There were no cases of lung cancer among the 222 smokers of pipes and cigars.

In the past 50 years Poland has experienced a rise in cigarette consumption and, more recently, a sharp rise in the incidence of and mortality from lung cancer (*16, 34*). In the 5-year period between 1963 and 1967, the mortality rate from lung cancer for men rose from 33.0 to 49.1 per 100,000. This increase was more pronounced in urban areas. Lung cancer has been the leading cause of death from malignant neoplasms in Polish men since 1959.

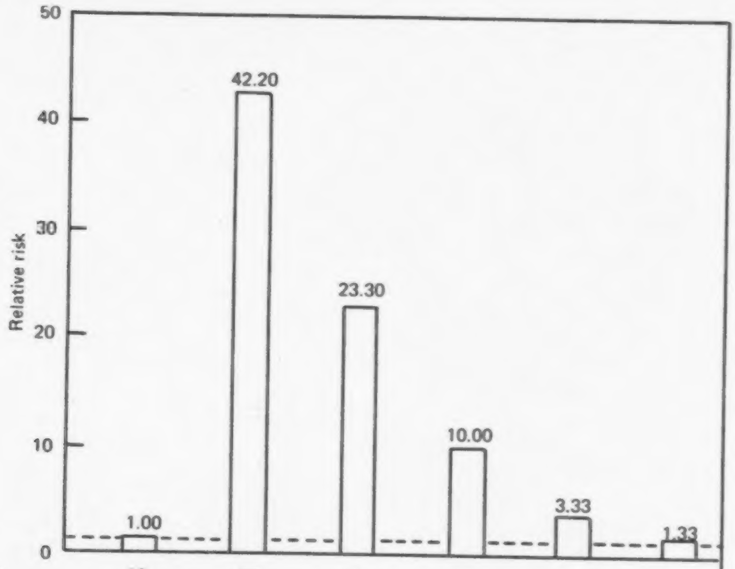
Additional studies conducted in Germany (*26*), Lebanon (*1*), Scotland (*6*), and Sweden (*37*) have demonstrated a strong association between cigarette smoking and lung cancer.

Rimington (*28*) examined the smoking habits and sputum production of 21,579 British males aged 40 and older who were screened for lung cancer by X-ray examination. During the follow-up period of 36 to 56 months, 64 new cases of lung cancer were identified. Because chronic bronchitis and lung cancer are both associated with cigarette smoking, the data were standardized by cigarette consumption categories. An increase in both lung cancer and chronic bronchitis was demonstrated with increasing consumption, but for each level of smoking there was a higher incidence of lung cancer among the individuals with chronic bronchitis than among those without this condition. Standardization with respect to age showed that the differences in lung cancer incidence between those with and without chronic bronchitis could not be accounted for by the increase seen in these diseases with advancing age. It was concluded that persons who smoke run a higher risk of chronic bronchitis than nonsmokers and those smokers who develop chronic bronchitis run a higher risk of developing lung cancer than smokers without chronic bronchitis. The relationship between lung cancer and chronic bronchitis was not demonstrated for pipe smokers.

Graham and Levin (*7*) examined the effect of cessation of cigarette smoking on the risk of developing lung cancer in a retrospective study of 700 lung cancer patients. The risk of developing lung cancer in ex-smokers declined sharply after cessation (figure 2). The decline occurred both in those who smoked for less than 31 years and those who had smoked 31 years or more (figure 3). Those who had smoked for less than 31 years had a lower risk of lung cancer following cessation than those with the longer smoking history in each category of time following cessation. Although there was an appearance of a somewhat more rapid rate of decline in risk with time following cessation for those who smoked for the shorter period, the difference was not statistically significant. The relative risk for the development of lung cancer for pipe and cigar smokers was 2.6. The reduction in risk following cessation of these forms of smoking was not examined.

The relationship of smoking to lung cancer in women has recently been examined by several authors. The smoking patterns of 142,857

Japanese women were described by Hirayama (*10*). Only 10.9 percent were daily smokers of cigarettes. Women started smoking at an older age than men and, in contrast to Western populations, there was a higher percentage of smokers in the older age groups than among younger women. The mortality rates were lower for women than for men, but a dose-response relationship was demonstrated. The lung cancer mortality ratio for women smokers of 1 to 9 cigarettes a day was 2.65 and rose to 3.14 for smokers of 20 to 24 cigarettes a day compared to nonsmokers.



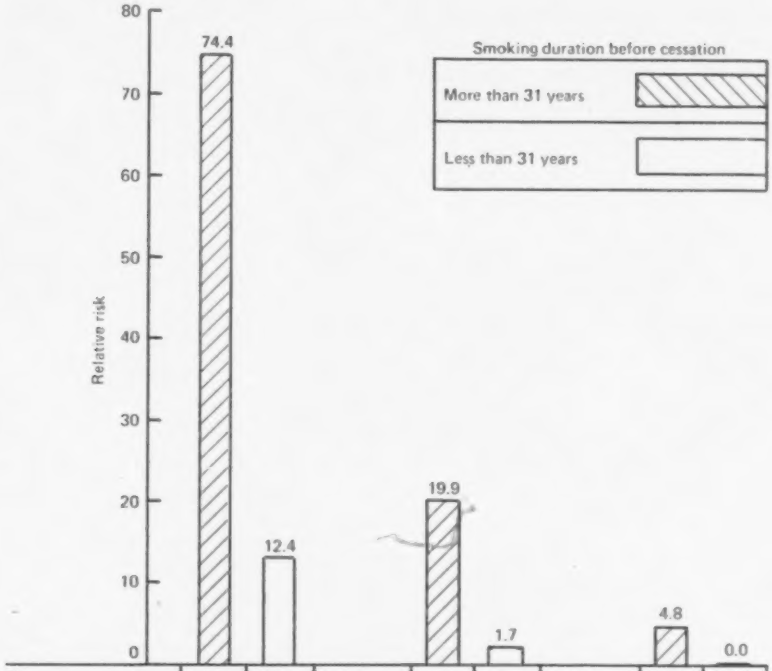
Cases	18	65	19	12	5	2
Controls	346	31	17	23	29	30
Months	Never Smoked	0-6	7-12	13-36	37-120	>120

(Smoked cigarettes only or with other forms and stopped all.)

FIGURE 2.—Relative risk of lung cancer in ex-smokers of cigarettes by length of cessation before diagnosis.

SOURCE: Graham, S., Levin, M. L. (7).

In two recent investigations (*9, 13*), both similar in design, the authors described higher rates of lung cancer among Jewish women in Pittsburgh and Montreal than among Catholic and Protestant controls. The proportion of epidermoid and anaplastic carcinomas was found to be lower for the 87 Jewish women with lung cancer in these studies than for the non-Jewish women. A survey of smoking habits in the two cities suggested that the increased incidence of lung cancer in Jewish women could not be entirely attributed to variations in smoking patterns. A low incidence of lung cancer was found among Jewish males, and this was correlated with their low cigarette consumption.



Cases	93	20		29	3		4	0
Controls	24	31		28	34		16	34
Years	0-1			2-10			>10	

(Smoked cigarettes only or with other forms and stopped all.)

FIGURE 3.—Relative risk of lung cancer in ex-smokers of cigarettes by length of cessation and previous duration of smoking.

SOURCE: Graham, S., Levin, M. L. (7).

The increased risk for the development of lung cancer among uranium miners is well established. The 1971 report, "The Health Consequences of Smoking" (*39*), summarized the recent investigations in this area. The histologic types of 121 cases of lung cancer in American uranium miners were studied by Saccomanno, et al. (*30*) using the WHO classification of lung tumors. A marked increase was noted in the small cell undifferentiated types with increasing radiation exposure. The author examined the role of tobacco in the etiology of these tumors stating, "... among uranium miners, cigarette smoking is a potent co-carcinogen in the cause of lung cancer, but exerts little, if any, influence on the cell type of lung cancer. . . ."

EXPERIMENTAL ASPECTS

Chemicals present in the particulate phase of tobacco smoke have been tested for their carcinogenic potential in experimental animals and/or tissue and organ cultures and have been grouped according to the type of activity observed. On mouse skin, certain chemicals induce tumor formation and are called *complete carcinogens;* others appear to act only in conjunction with additional treatment, and are referred to as *incomplete carcinogens.* They include *tumor initiators* and *tumor promoters. Tumor initiators* induce an irreversible change in epidermal cells which causes them to respond to subsequent applications of *tumor promoters* with the development of skin tumors. This two-stage mechanism of carcinogenesis, well known for mouse skin, has not been demonstrated in other animal species or tissues under comparable conditions.

Hoffmann and Wynder (*11, 44*) discussed the major initiators and promoters found in cigarette smoke and described an additional property of *acceleration* possessed by N-alkylated carbazoles, N-alkylated indoles, and Trans-4, 4′-dichlorostribene (DCS) which is a pyrolysis product of the insecticides DDT and DDD. These compounds are inactive as complete carcinogens, initiators, or promoters but accelerate the initiator-promoter activity of polynuclear aromatic hydrocarbons (PAH).

The initiating activity of polycyclic aromatic hydrocarbons in two-stage carcinogenesis was investigated and reviewed by Van Duuren, et al. (*41*). Several compounds previously thought to be of little or no significance in tobacco carcinogenesis have been found by Van Duuren and other independent investigators to be tumor *initiators.* Table 1 lists a number of these compounds. Tumor *promoting* agents probably allow these weak carcinogens to express their tumorigenic potential. Dibenz(a, c)anthracene which was reported by Van Duuren, et al. (*41*) to be an *initiating* agent was found by Lijinsky, et al. (*22*) to also act as a *complete carcinogen* in mouse skin experiments.

In another investigation, Van Duuren, et al. (*42*) confirmed that tobacco smoke condensate is primarily a tumor-promoting agent with weak carcinogenic activity. They also found that benzo(a)-pyrene, a carcinogen in cigarette "tar," acts as a tumor promoter when applied to mouse skin in low doses over a long time period

TABLE 1.—*Some initiating agents in two-stage carcinogenesis.*

Compound
† Dibenz(a,c)anthracene
† Chrysene
† Benz(a)anthracene
† 6–Methylanthanthrene
Chloromethyl methyl ether
Urethan
Triethylenemelamine
1,4–Dimethanesulfonoxy–2–butyne

† Those found in cigarette smoke.

SOURCE: Van Duuren, et al. (41).

after the application of an initiating agent. This supports the observation that the tumor-promoting activity of cigarette "tar" may represent the summation of carcinogenic activities of the several carcinogenic aromatic hydrocarbons present in cigarette "tar."

In tobacco carcinogenesis research the choice of bioassay is of major importance. Mouse and rabbit skin models have been an important source of experimental data concerning tobacco carcinogenesis (*44*). Several relatively rapid screening bioassays have been recently suggested. Major (*24*) examined the effects of tumor promoters and initiators on mouse skin, measuring cell numbers, cell size, mitotic index, and epidermal thickness. Changes found during the first five days were characteristic for different agents.

The effects of polycyclic aromatic hydrocarbons on the nonspecific esterase activity in sebaceous glands of mice were examined by Healey, et al. (*8*). The changes observed were not entirely specific for carcinogenic activity and were probably related more to the toxicity of the painted substances to the sebaceous gland cells. This suggests that further improvement is needed in this system before it can be a practical screening bioassay for potential carcinogenic compounds.

Shabad (*33*) reviewed experimental studies from Russia and elsewhere relating tobacco with tumor formation, and concluded, "... it is indicated that cigarette smoke can actually induce lung cancer in animals."

Leuchtenberger and Leuchtenberger (*21*) have described adenomas and adenocarcinomas in the lungs of mice chronically exposed to cigarette smoke.

Takayama (*36*) found that subcutaneous injections of cigarette "tar" in newborn mice produced benign and malignant tumors of the liver, lung, and lymphoid tissue.

The compound 7H-Dibenz(c,g)carbazole (7H-DBC), a component of cigarette smoke, was tested for its carcinogenic potential on the respiratory tract of Syrian golden hamsters using 15 or 30 intratracheal injections per week. Sellakumar and Shubik (*32*) found a high percentage of squamous tumors of the trachea and bronchi in the tested animals and observed that 7H-DBC appeared to be a potent carcinogen for the respiratory system of hamsters.

Krasnyanskaya (*18*) has examined the effects of chronic exposure to cigarette smoke on the respiratory tract of 95 rabbits. One group was pretreated with an intratracheal injection of benz(a)-pyrene. Although premalignant changes were found in treated animals, no malignancies were observed after four years of exposure.

OTHER CANCERS

The relationships between tobacco smoking in its various forms and cancers of the oral cavity, larynx, esophagus, kidney, urinary bladder, and pancreas were summarized in the 1971 report, "The Health Consequences of Smoking" (*39*).

1. *Cancer of the Larynx*
   a. Epidemiological, experimental, and pathological studies support the conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx.

   b. The risk of developing laryngeal cancer among cigarette smokers as well as pipe and/or cigar smokers is significantly higher than among nonsmokers.

   c. The magnitude of the risk for pipe and cigar smokers is about the same order as that for cigarette smokers, or possibly slightly lower.

   d. Experimental exposure to the passive inhalation of cigarette smoke has been observed to produce premalignant and malignant changes in the larynx of hamsters.

2. *Cancer of the Oral Cavity*
   a. Epidemiological and experimental studies contribute to the conclusion that smoking is a significant factor in the development of cancer of the oral cavity and that pipe smoking, alone or in conjunction with other forms of tobacco use, is causally related to cancer of the lip.

   b. Experimental studies suggest that tobacco extracts and tobacco smoke contain initiators and promoters of cancerous changes in the oral cavity.

3. *Cancer of the Esophagus*
   a. Epidemiological studies have demonstrated that cigarette smoking is associated with the development of cancer of the esophagus.
   b. The risk of developing esophageal cancer among pipe and/or cigar smokers is greater than that for nonsmokers and of about the same order of magnitude as for cigarette smokers, or perhaps slightly lower.
   c. Epidemiological studies have also indicated an association between esophageal cancer and alcohol consumption and that alcohol consumption may interact with cigarette smoking. This combination of exposures is associated with especially high rates of cancer of the esophagus.
4. *Cancer of the Urinary Bladder*
   a. Epidemiological studies have demonstrated an association of cigarette smoking with cancer of the urinary bladder among men.
   b. The association of tobacco usage and cancer of the kidney is less clear-cut.
   c. Clinical and pathological studies have suggested that tobacco smoking may be related to alterations in the metabolism of tryptophan and may in this way contribute to the development of urinary tract cancer.
5. *Cancer of the Pancreas*

   Epidemiological studies have suggested an association between cigarette smoking and cancer of the pancreas. The significance of the relationship is not clear at this time.

Additional relevant epidemiological, pathological, and experimental data have been reported.

CANCER OF THE LARYNX

McNelis and Esparza (*23*) reported 14 cases of carcinoma *in situ* of the larynx found among 387 vocal cord biopsies. Thirteen patients were men and with one exception all smoked cigarettes.

Lavelle (*20*) described 11 patients with carcinoma of the larynx which occurred as a second primary cancer at least one year after the successful treatment of an initial primary cancer of the bronchus. "Although it was not possible to ascertain with certainty the smoking habit of all these patients there were no definite nonsmokers among them."

ORAL CANCER

Leukoplakia of the oral mucosa represents a keratinization of surfaces normally unkeratinized. Over a 23-year period, Sugar and Banoczy (*35*) observed 535 patients with leukoplakia. Of the 324 patients examined in the latest survey, 96 (30 percent) had leukoplakia for more than 10 years. Two hundred sixty-nine patients (83 percent) were smokers. Treatment was ineffective in those patients who continued to smoke. Oral cancer eventually developed in 13 of 48 patients (27 percent) who had severe leukoplakia.

The initial changes in the mouth caused by smoking may not be the hyperkeratotic lesions of leukoplakia. Meyer, Rubinstein, and colleagues (*25, 29*) examined the effects of smoking on the surface cytology of clinically normal oral mucosa and, in general, found that smoking produced changes in cytoplasm characterized by less mature cell configurations. These changes were most pronounced on those surfaces most directly exposed to the stream of cigarette smoke.

Etiological aspects of squamous cancers of the head and neck were reviewed by Wynder (*43*). There was an increased likelihood of a second primary tumor forming at the site of the first cancer if a patient had been a heavy smoker, or if he continued to smoke, after surgical removal of the first primary. From a preventive point of view it was observed that squamous cell cancers of the head and neck would be comparatively rare in the absence of tobacco and excessive alcohol consumption.

Jussawalla and Deshpande (*15*) examined various types of smoking and chewing habits in a retrospective investigation of 2,005 patients in Bombay, India, who had histologically established cancers of the oral cavity, pharynx, larynx, and esophagus. Smokers used either a manufactured cigarette or the Indian "bidi" which contains a small quantity of shredded tobacco rolled in a dried leaf, usually of the Temburni tree (*Dispyros Melanoxylon*). Chewers used "pan" made with betel leaf, lime, and spices. A small quantity of tobacco was, on occasion, added to this mixture as an optional ingredient. Smoking and chewing both resulted in an increased risk of cancer at each site examined with a striking increase in risk observed in patients who had the combined habits of chewing and smoking (figure 4). The independent contribution of tobacco to the increased risk of cancer at each site could not be clearly isolated as there was no control for chewing when smoking characteristics were examined and vice versa.

Intra-oral smoking with the lighted end of a cigar or cigarette inside the mouth is a custom found in parts of the Caribbean, South America, India, and the Island of Sardinia. Morrow and Suarez

(*27*) examined 79 intra-oral smokers, most of whom had sought medical attention for reasons other than symptoms associated with smoking-related diseases. All but one patient demonstrated "nicotinic stomatitis" characterized by hyperplasia, acanthosis, hyperkeratosis, and parakeratosis. Sixteen cases of squamous cell carcinoma were found. These were located predominantly at the base of the tongue, tonsillar fauces, and adjacent pharyngeal mucosa.

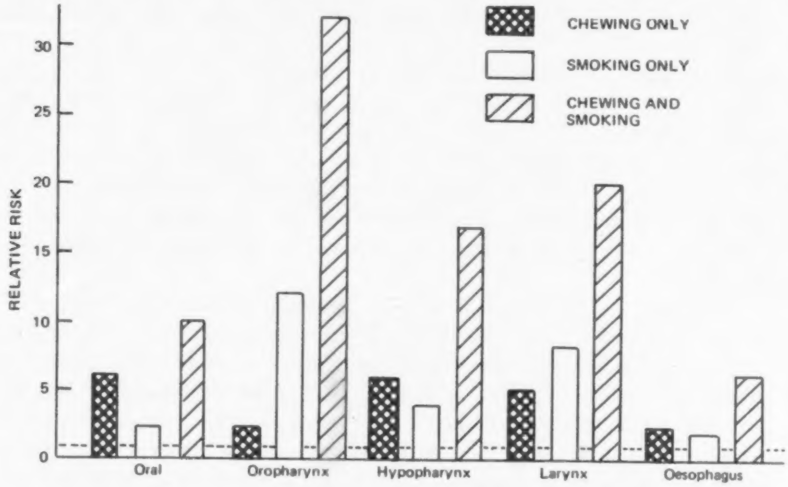


FIGURE 4.—Relative risk of cancer of the oral cavity, pharynx, larynx, and esophagus associated with smoking and chewing in various forms.

SOURCE: Jussawalla, D. J., Deshpande, V. A. (15).

The oral mucosa of many experimental animals appears to be resistant to the induction of cancers. Cohen, et al. (*4*) failed to produce any distinctive cancerous or precancerous changes in the mucosal lining of surgically created buccal pouches of monkeys filled with chewing tobacco for varying lengths of time. Homburger (*12*) exposed the oral mucosa of Syrian golden hamsters to snuff and 7,12-Dimethylbenz(a)anthracene (DMBA) using a bit inserted in the mouth. Snuff alone failed to produce any changes that were not also seen in the control animals who had a plain cotton plug inserted in the mouth. Benzo(a)pyrene and DMBA caused a few carcinomas of the oral mucosa, but they produced a much higher number of cancers outside the mouth where the carcinogenic agents had spilled onto the perioral skin. The authors observed that "... skin-painting experiments are more sensitive indicators of carcinogenicity for the oral mucosa than applications to the mucosa itself."

CANCER OF THE ESOPHAGUS

Cancer of the esophagus is associated with both tobacco and alcohol consumption.

In the prospective study from Japan, Hirayama (*10*) found no significant association between the use of cigarettes or alcohol alone and cancer of the esophagus, but there were high rates of esophageal cancer among individuals using both cigarettes and alcohol (figure 5).

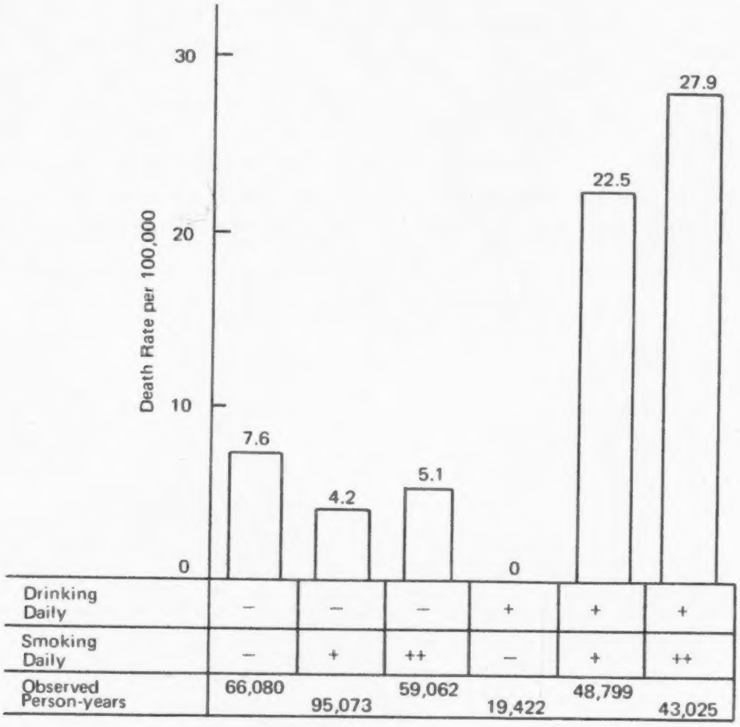


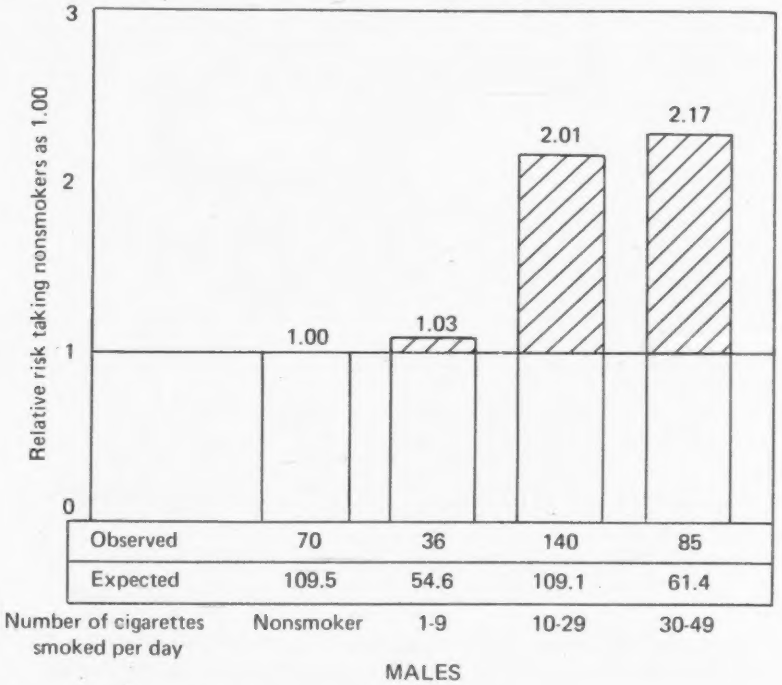
FIGURE 5.—Death rates for cancer of the esophagus in Japanese males by smoking and drinking characteristics.

SOURCE: Hirayama, T. (10).

Schoenberg, et al. (*31*), using cohort analysis, examined mortality from esophageal cancer in the United States. Substantial ethnic, geographic, and temporal variations were observed. On a state-by-state basis, mortality from esophageal cancer was correlated about equally with urbanization, per capita cigarette sales, and per capita alcohol sales. The correlation with urbanization was partially explained by increased sales of tobacco and alcohol in urban areas.

CANCER OF THE URINARY BLADDER

In a retrospective study of 470 confirmed cases of transitional cell or squamous cell cancers of the bladder, Cole, et al. (*5*) found a consistent positive relationship between cigarette smoking and bladder cancer. The relative risk and standard error for the development of bladder cancer were 1.89 ± 0.22 for male smokers and 2.00 ± 0.33 for female smokers. A dose-response relationship was demonstrated for both the number of cigarettes smoked per day (figures 6 and 7) and various degrees of inhalation. Bladder cancer has been shown to be associated with certain occupational categories such as dye workers, certain textile workers, tailors, and nurses (*2, 14*). Cole standardized the data with respect to occupation and found that the risk demonstrated could not be explained by any indirect association with industrial exposure. Cole concluded: "The



Number of cigarettes smoked per day	Nonsmoker	1-9	10-29	30-49
Observed	70	36	140	85
Expected	109.5	54.6	109.1	61.4

FIGURE 6.—Relative risk of urinary bladder cancer for males by amount smoked.

SOURCE: Cole, P., et al. (5).

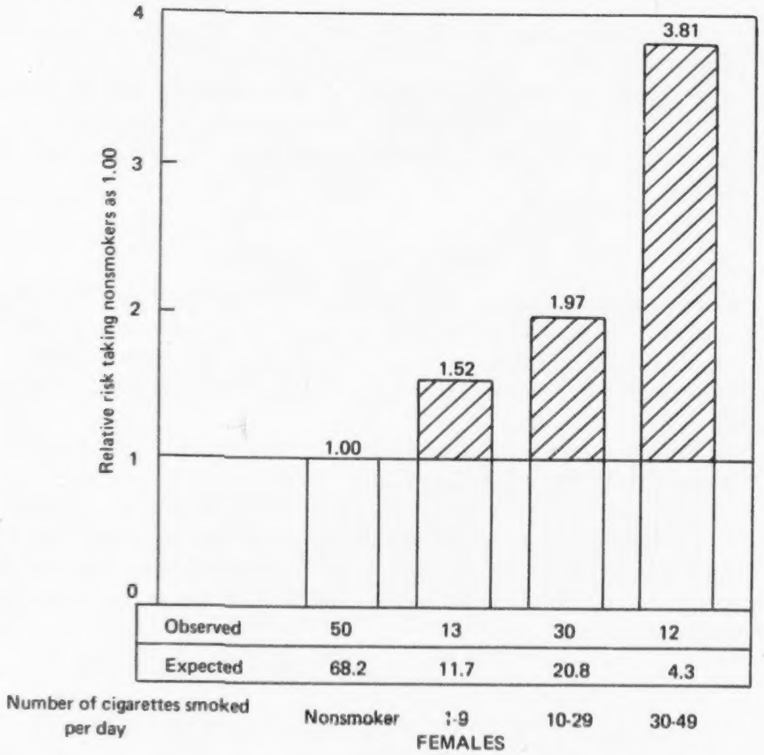


FIGURE 7.—Relative risk of urinary bladder cancer for females by amount smoked.

SOURCE: Cole, P., et al. (5).

present findings indicate that about 35 percent of cases of cancer of the lower urinary tract in the study population are associated with cigarette smoking. If this association is accepted as causal, and if it is generalized to the entire population of the United States, smoking is associated with about 3,100 deaths per year from cancer of the lower urinary tract." No significant association was found between pipe or cigar smoking and bladder cancer.

Tyrrell, et al. (*38*) examined several factors including smoking history and occupation in a group of 250 patients treated for urinary bladder cancer in Ireland. No significant association between occupation and bladder cancer was found. This may have been due to the low concentration of high-risk industries for this cancer in Ireland. A significant ($P < 0.005$) association was found in males between cigarette smoking and cancer of the urinary bladder, but no significant association was found for the 50 cases of bladder cancer in females.

In an extensive review of cancer of the urinary tract, Clayson and Cooper (*3*) included data that demonstrated an association between cigarette smoking and excessive mortality from bladder cancer.

CANCER OF THE PANCREAS

Cancer of the pancreas was responsible for 9,696 deaths among men and 7,190 deaths among women in the United States in 1967 (*40*). The United States age-adjusted mortality rate for carcinoma of the pancreas has risen from 2.9 to 8.2 per 100,000 from 1920 to 1965 (*17*).

In the prospective Japanese study by Hirayama (*10*), the preliminary data showed a pancreatic cancer mortality ratio of 2.7 for male smokers and a mortality ratio of 3.0 for female smokers.

In an epidemiologic appraisal of cancer of the pancreas, Krain (*17*) found that cigarette smoking and industrial exposure were more strongly associated with this disease than either air pollution or genetic factors.

HIGHLIGHTS OF CURRENT CANCER INFORMATION

In addition to the comprehensive summary from the 1971 report, "The Health Consequences of Smoking" (*39*), cited earlier in this chapter, the following statements are made to emphasize the most recent developments in the field:

1. Preliminary results from a major prospective epidemiological study in Japan demonstrate a strong association between cigarette smoking and lung cancer. A dose-response relationship was demonstrated for the number of cigarettes smoked. These findings in an Asian population with distinct genetic and cultural characteristics confirm the major importance of cigarette smoking in the causation of lung cancer, a conclusion which up to now has been based largely on studies of Caucasian populations in the United States, Canada, and Europe.

2. Ex-smokers have significantly lower death rates for lung cancer than continuing smokers. The decline in risk following cessation appears to be rapid both for those who have smoked for long periods of time and for those with a shorter smoking

history, with the sharpest reductions taking place after the first two years of cessation.

3. The risk of developing lung cancer appears to be higher for smokers who have chronic bronchitis. Though both conditions are directly related to the amount and duration of smoking, an additional risk for lung cancer appears to exist for cigarette smokers with chronic bronchitis which is independent of age and number of cigarettes consumed.

4. Experimental studies on animals have demonstrated that the particulate phase of tobacco smoke contains certain chemical compounds which can act as complete carcinogens, tumor initiators, or tumor promoters. Recently, other compounds have been described that have no independent activity in two-stage carcinogenesis but *accelerate* the carcinogenic effects of polynuclear aromatic hydrocarbons in the initiator-promoter system.

5. Additional epidemiological evidence confirms a significant association between the combined use of cigarettes and alcohol, and cancer of the esophagus.

6. Epidemiological studies have demonstrated a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the risk of developing bladder cancer increases with inhalation and the number of cigarettes smoked.

7. Epidemiological evidence demonstrates a significant association between cigarette smoking and cancer of the pancreas.

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CHAPTER 5

Pregnancy

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INTRODUCTION

The 1971 report, "The Health Consequences of Smoking" (*23*), summarized the relationship between smoking and pregnancy as follows:

> Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birth weight and an increased incidence of prematurity, defined by weight alone. There is strong evidence to support the view that smoking mothers have a significantly greater number of unsuccessful pregnancies due to stillbirth and neonatal death as compared to nonsmoking mothers. There is insufficient evidence to support a comparable statement for abortions. The recently published Second Report of the 1958 British Perinatal Mortality Survey, a carefully designed and controlled prospective study involving large numbers of patients, adds further support to these conclusions.

New epidemiological, experimental, and pathologic studies lend support to the foregoing statements.

EFFECT ON BIRTH WEIGHT

Analysis of data from more than 100,000 births has shown that infants of mothers who smoke during pregnancy have a mean birth weight of 6.1 ounces (173 grams) less than infants born to nonsmoking mothers (*23*). Several recent studies confirm this relationship (*1, 2, 6, 7, 10, 13, 15, 18, 25*).

EFFECT ON THE OUTCOME OF PREGNANCY

New studies have been published concerning the effect of maternal smoking on the outcome of pregnancy.

Kullander and Källen (*13*) performed a prospective study in Sweden involving 6,363 pregnant women. These women completed several questionnaires during the course of their pregnancy, and in this manner specific information was obtained on smoking habits for the entire pregnancy. Forty-four percent of the women smoked cigarettes during pregnancy and 97 percent of these smoked during the whole pregnancy.

Stillbirths, neonatal deaths, and deaths occurring before one year of age were recorded to determine a "total death risk." This risk was approximately 60 percent higher for children born to smoking mothers as compared to those born to nonsmoking mothers.

Deaths occurring before one week of age and also deaths taking place between the age of one week and one year were significantly more frequent in children born to smoking mothers. Among children dying before one week of age, significantly more cases of abruptio placentae were found in smoking mothers than in nonsmoking mothers. The higher level of neonatal mortality in children born to smoking mothers was confined to those weighing more than 2,500 grams. Live-born infants weighing less than 2,500 grams had equally high neonatal mortality rates whether they were born to smoking or nonsmoking mothers. The stillbirth rate was greater in smoking mothers than in nonsmoking mothers, but the difference was not statistically significant.

An overall increased risk of spontaneous abortion among smoking women was found, but this was primarily due to an association between unwanted pregnancy and smoking. The authors found that significantly ($P < .001$) more women with unwanted pregnancies were smokers than women with wanted pregnancies; in addition, spontaneous abortions were significantly ($P < .001$) more frequent among women with unwanted pregnancies than among women with wanted pregnancies. When correction was made for the mothers' acceptance of pregnancy, the contribution of maternal smoking to spontaneous abortion was of only borderline significance.

Also in the Kullander and Källen study (*13*), a decreased frequency of preeclampsia among smoking mothers was noted. Maternal smoking had no effect on the mean Apgar score of surviving, non-malformed children.

A prospective study from Sweden of abortions in 4,312 pregnancies was reported by Palmgren and Wallander (*17*). Only those women who smoked throughout pregnancy were considered smokers. The lowest abortion rate was found among nonsmokers, 7.8 percent, while the highest rate was found among heavy smokers, 14.5 percent (table 1). The difference is statistically significant ($P < .001$). Heavier smokers appeared to abort earlier in pregnancy. A history of previous abortion was obtained twice as often in heavy smokers as in nonsmokers.

Yerushalmy reported in 1964 on pregnancies occurring in women participating in the Kaiser Health Plan of the San Francisco-Oakland area (*24*). The 1971 report, "The Health Consequences of Smoking" (*23*), commented in detail on that report. Recently, Yerushalmy published data on 13,083 pregnancies occurring in this plan between 1960 and 1967, which included the 6,800 cases previously reported (*24*, *25*).

TABLE 1.—*Frequency of abortion and cigarette consumption.*

Result of the pregnancy	Nonsmokers	≦10 cigarettes	>10 cigarettes	Total
Abortion	177 7.8%	148 9.1%	60 14.5%	385 8.9%
Delivery	2,087 92.2%	1,486 90.9%	354 85.5%	3,927 91.1%
Total	2,264	1,634	414	4,312

SOURCE: Palmgren, B., Wallander, B. (17).

As in the 1964 study, he again found an increase in the incidence of low birth weight infants (less than 2,500 grams) among smoking mothers. These small infants had a significantly lower neonatal mortality rate and fewer congenital anomalies than the small infants born to nonsmoking mothers. The neonatal mortality rate for single, live-born infants born to white, smoking mothers was 11.3/1000, while that for single, live-born infants born to white, nonsmoking mothers was 11.0/1000; the difference is not significant.

Taylor analyzed Yerushalmy's data for the probability of fetal death and found no difference between smoking and nonsmoking mothers (*22*).

Some of these findings are different from those reported in the other recent, large-scale prospective studies (*5*, *13*, *17*, *19*), and some of the differences may be a consequence of the definition of "smoker" used. In the study of Kullander and Källen (*13*), multiple interviews were performed during pregnancy which allowed more precise separation of the pregnant women into smokers and nonsmokers. In the study reported by Palmgren and Wallander (*17*), only those women who smoked throughout pregnancy were considered smokers. The British Perinatal Mortality Study (*5*), which was discussed in the 1971 report, "The Health Consequences of Smoking" (*23*), defined "smokers" as those women who smoked regularly after the fourth month of pregnancy. The smoking history was obtained shortly after delivery of the infant.

In contrast, Yerushalmy (*25*) defined "smokers" as women who were smoking one or more cigarettes a day during the pregnancy, and "nonsmokers" as women who never smoked and those who stopped smoking either before or during the pregnancy. Because the smoking history was obtained only once, usually early in pregnancy, some of the women who were classified as smokers could have gone through a significant portion of their pregnancy as nonsmokers, and similarly some of the women who were classified as nonsmokers could have gone through a significant portion of their pregnancy as smokers. If smoking by pregnant women increases the risk of an unsuccessful pregnancy, an imprecise separation of pregnant women into smokers and nonsmokers would tend to diminish the magnitude of any differences found. One Swedish study (*13*) and the British Perinatal Mortality Study (*5*) seemed to be at variance in statements about the frequency with which smoking habits vary from one portion of the pregnancy to another. If this is a culturally determined phenomenon, there is no way of estimating the extent to which it applies to the patients participating in the Kaiser Health Plan described by Yerushalmy.

MacMahon, et al. (*14*) commented on Yerushalmy's analysis of mortality rates in low birth weight infants. They observed that there are "... factors that affect birth weight without influencing mortality; for example, females have lower birth weights than males but not the higher mortalities that might be predicted for them on that account. If cigarette smoking is another such factor, the explanation of the higher weight-specific mortalities for nonsmokers becomes immediately clear: it is an artifact of the analysis. It is meaningful to compare category-specific rates only when the specification of the category has the same implication for each of the populations compared."

Perinatal mortality rates were similar in infants born to smoking and nonsmoking mothers in a recent prospective investigation of 1,300 pregnancies from New Zealand (*1*). Women were classified as smokers or nonsmokers during their first "booking" at an antenatal clinic, and this was not later amended. This method of classification is similar to that used in the Yerushalmy study.

Comstock, et al. (*6, 7*) have reported in 1967 and 1971 on the relationship of maternal smoking to the outcome of pregnancy. In their studies, all perinatal deaths and samples of live births occurring during a 10-year period among children whose mothers were residents of Washington County, Maryland, were matched against the records of a special census based on a household interview taken in 1963. Maternal smokers were defined as women who were smoking in 1963 and who had started to smoke prior to the pregnancy in question; maternal nonsmokers were women who denied ever having smoked. When this study is compared to previously cited studies (*5, 13, 17*), the data on the smoking status of the mothers during pregnancy are imprecise, which limits their value.

In the 1967 study (*6*), maternal smoking was associated with an increased risk of mortality for the child, both in the neonatal period and for several years thereafter; however, this effect was thought to be related to factors such as adequacy of prenatal or postnatal environment and care, rather than a direct effect of maternal smoking. Stillbirth rates were similar for smokers and nonsmokers.

The more recently published study (*7*) includes a 32 percent sample of live-born, low birth weight infants and a 3 percent sample of live-born, larger infants born during the 10-year period preceding the census. The total births represented by these samples were 4,641 to smokers and 7,646 to nonsmokers. The neonatal mortality rate, when adjusted for environmental and socioeconomic factors, was approximately one-third higher among infants born to smoking mothers than among those born to nonsmoking mothers (*7*). The categories of asphyxia, atelectasis, and immaturity accounted for the greater neonatal mortality among infants born to smoking mothers as compared to those born to nonsmoking mothers (*7*).

CONGENITAL MALFORMATIONS

As noted in the 1971 report, "The Health Consequences of Smoking" (*23*), the possible teratogenic effect of maternal smoking has not been adequately evaluated. Additional studies have been published in the interim, but rather than investigating congenital malformations in both stillborn and live-born infants, most of the recent studies have dealt only with live-born infants.

Fedrick, et al. (*8*) analyzed data from the large British Perinatal Mortality Study for the incidence of congenital heart disease in stillborn and live-born infants of smoking and nonsmoking mothers. An incidence of 7.3/1000 births was found in infants born to smoking mothers as compared to 4.7/1000 births for infants born to nonsmoking mothers, a statistically significant difference ($P < .001$).

Kullander and Källen (*13*) noted no teratogenic effect of maternal smoking in children dying before one year of age or in children surviving one year of age. However, they observed that published studies have been too small to exclude this possibility.

In a study of perinatal death occurring in infants weighing more than 1,000 grams, Bailey (*1*) found that maternal smoking did not lead to an increased incidence of congenital anomalies.

Yerushalmy (*25*) reported only on live-born infants weighing less than 2,500 grams and found significantly fewer ($P < .02$) anomalies among infants born to smoking mothers.

Comstock, et al. (*7*) found fewer than the expected number of congenital anomalies among live-born infants of smoking mothers.

CANCER IN CHILDREN BORN TO SMOKING MOTHERS

Neutel and Buck (*16*) studied the relationship between maternal smoking during pregnancy and the development of cancer in the offspring. The base population was obtained from the British and Ontario Perinatal Studies and consisted of 89,302 babies who survived at least seven days. There were 65 cancer deaths and 32 cancer survivors in the period from birth to a minimum of 7 and a maximum of 10 years of age. For cancer of all sites, the children of smokers had a relative risk of 1.3. The authors concluded: "Although these results make it most unlikely that *in utero* exposure to tobacco smoke has a broadly carcinogenic effect on the fetus, a response confined to one tissue or expressed over a narrow age range cannot be ruled out."

LONG-TERM EFFECTS ON CHILDREN BORN TO SMOKING MOTHERS

Goldstein (*9*) analyzed data from the British Perinatal Mortality Study to determine factors influencing the height of 7-year-old children. In the 1958 study, information was collected on 16,994 singleton births. In 1965, heights were measured "to the nearest inch" on 13,127 of these children who could be followed up. The data were analyzed for the influence of parity, birth weight, length of gestation, maternal age, maternal height, social class, number of younger siblings, and maternal smoking habits during pregnancy. Allowance was made for the sex and age of the child at the time of measurement. The author's conclusions included the following: "After allowing for the other variables, the children of mothers who smoked 10 or more cigarettes a day after the 4th month of pregnancy, are on average about 1.0 cm shorter at age seven than the children of mothers who did not smoke."

EXPERIMENTAL STUDIES

Becker and Martin (*3*) continued their experiments concerning the effect of nicotine on pregnant rats. Offspring of rats given nicotine weighed significantly less at birth than saline-injected controls. There were fewer live births among the nicotine-injected rats.

Kelly and Roy (*12*), using cinephotomicrography, demonstrated that nicotine crosses the mouse placental barrier in amounts adequate to produce a measurable cardiovascular response.

Stalhandske, et al. (*21*) studied the *in vitro* metabolism of nicotine in livers of fetal, young, and adult mice. Cotinine was found to be the major metabolite at all ages investigated.

Using radioactive compounds, Sieber and Fabro (*20*) identified a variety of drugs in the preimplantation blastocyst and in uterine secretions of pregnant rabbits. In animals receiving dose levels of nicotine comparable to that encountered in man, significant amounts of radioactivity were found in the preimplantation blastocyst. A markedly higher concentration of radioactivity was observed in uterine secretion than in maternal plasma.

Juchau (*11*) studied the levels of benzpyrene hydroxylase in the placentas of smoking and nonsmoking women obtained both early in pregnancy and at term. This enzyme hydroxylates benzo(a)pyrene, a carcinogenic hydrocarbon found in tobacco smoke. Previous studies had shown that placentas, obtained at term from smoking women, have a greater ability to hydroxylate benzo(a)pyrene than the placentas from nonsmokers (*23*). Juchau corroborated this, but also found very low levels in placental tissues obtained from healthy smokers during first trimester dilatation and curettage or hysterotomy for therapeutic abortion. This lack of significant placental drug metabolizing activity during the first trimester was interpreted as a possible hazard to the fetus, particularly if the substance were active in the unmetabolized form. Enzyme levels were undetectable in placental homogenates of nonsmokers at 8 to 16 weeks gestation.

The carcinogenic effect on the newborn of rats receiving benzo(a)pyrene during the latter half of pregnancy was studied by Bulay and Wattenberg (*4*). An increased incidence of pulmonary adenoma and skin papilloma was observed.

SUMMARY

Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birth weight and an increased incidence of prematurity, defined by weight. There is increasing evidence to support the view that women who smoke during pregnancy have a significantly greater risk of an unsuccessful pregnancy than those who do not.

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CHAPTER 6

Gastrointestinal Disorders

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GASTROINTESTINAL DISORDERS

The 1971 report, "The Health Consequences of Smoking" (*4*), summarized the relationship between smoking and peptic ulcer as follows:

> Cigarette smoking males have an increased prevalence of peptic ulcer disease and a greater peptic ulcer mortality ratio. These relationships are stronger for gastric ulcer than for duodenal ulcer. Smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of ulcer healing.

Studies of the effect of smoking on gastric secretion in patients with peptic ulcer and normal controls have produced conflicting reports (*4*). Recently, Wilkinson and Johnston (*5*) reported a significant inhibition of pentagastrin-stimulated gastric acid secretion after cigarette smoking by normal volunteers, while Debas, et al. (*1*) found no significant overall change. Wilkinson and Johnston also studied patients with gastric and duodenal ulcers in whom a significant inhibition of pentagastrin-stimulated gastric secretion was observed after the patients smoked one or two cigarettes over a period of 10 to 15 minutes.

A study by Konturek, et al. (*3*) suggests that alterations in pancreatic and biliary secretion may be responsible for the relationship between smoking and peptic ulcer. Nicotine was infused in mongrel dogs in doses corresponding to amounts absorbed from smoking up to four cigarettes in one hour. In the pancreas, nicotine inhibited the secretin-stimulated secretion of both fluid and bicarbonate, and the degree of inhibition was dose-related. Spontaneous biliary secretion of bicarbonate was also depressed by the drug. Nicotine had no effect on gastric secretion of acid, gastric mucosal blood flow, or the mucosal barrier to hydrogen or sodium ions. This inhibition of pancreatic and hepatic bicarbonate secretion may deprive the duodenum of sufficient alkaline secretion to neutralize gastric acidity and may be one biomechanism linking cigarette smoking and peptic ulcer.

Dennish and Castell (*2*) noted the clinical association between cigarette smoking and heartburn. To investigate the biomechanism of this relationship, lower-esophageal sphincter pressure determinations were made before and after smoking in six normal male volunteers. All of the volunteers were cigarette smokers. In each subject after the onset of cigarette smoking, there was a rapid decrease in lower-esophageal sphincter pressure from the basal level. This diminution in sphincter pressure persisted until smoking was stopped, at which time the pressure returned rapidly toward normal. Mean basal pressure was 19.6 ± 2.1 (± 1 S.E.) mmHg. and mean pressure during smoking was 11.4 ± 2.2 mmHg. The difference between these pressures is statistically significant ($P < .001$). No changes were noted when volunteers puffed on unlit cigarettes. Variable responses were noted when volunteers smoked cigars and pipes. The investigators concluded that cigarette smoking decreases the effectiveness of the lower-esophageal sphincter as a barrier against gastroesophageal reflux.

HIGHLIGHTS OF CURRENT GASTROINTESTINAL INFORMATION

In addition to the summary statement cited at the beginning of this section, the following observations have been made:

1. A possible link between cigarette smoking and peptic ulcer has been demonstrated in dogs in which nicotine was found to inhibit pancreatic and hepatic bicarbonate secretion. This could lead to peptic disease by depriving the duodenum of sufficient alkaline secretion to neutralize gastric acidity.
2. An investigation in human volunteers has suggested that cigarette smoking decreases the effectiveness of the lower-esophageal sphincter as a barrier against gastroesophageal reflux.

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CHAPTER 7

Allergy

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INTRODUCTION

As early as 1886 reference was made to an entity called "tobacco asthma" (*64*). Subsequently, controversy has arisen over whether tobacco smoking causes clinical allergy (*61*) and whether such tobacco allergy is associated with the major smoking-related diseases (*25, 69*).

In 1957, Silvette, et al. (*64*) reviewed more than 100 papers concerned with "the immunological aspects of tobacco and smoking." They concluded that inadequate animal studies had been performed in this area. Referring to clinical studies, they observed: "... virtually all reported clinical investigation has been limited to determinations of cutaneous sensitivity to tobacco extracts; and it must be regretfully admitted that much of this published work is equivocal, uncritical, and inadequately controlled."

Such criticism is also applicable to many studies published since then.

Epidemiologic studies designed to determine the prevalence of tobacco allergy have not been carried out; hence, it is difficult to evaluate the magnitude of the problem.

Allergy may be defined as a specific alteration in response mediated by an antigen-antibody reaction. When a hereditary susceptibility to allergic illness is present, the term atopy is used. For example, hay fever and asthma are atopic diseases.

There is no single test or observation which can be used to determine whether a substance may be responsible for allergic disease; however, fulfillment of the following criteria constitutes evidence for such a relationship:

1. Demonstration that the substance is antigenic, i.e., capable of stimulating the production of antibody and then reacting with the antibody.
2. Demonstration that, upon exposure to the substance, signs and symptoms simulating an allergic reaction are elicited which disappear upon its removal.
3. Demonstration that the immunologic event is related to the clinical event.

Recent advances in the understanding of immunological reactions as well as in the methodology of immunology are now being applied to problems of clinical allergy. For example, Ishizaka (*37*), using radioimmunoelectrophoresis, recently reported that the so-called "allergic antibody" (reagin, skin-sensitizing antibody (SSA), atopic antibody) belongs to a new class of immunoglobulins, IgE.

Although the skin test remains a simple and definitive method of demonstrating reagins in the allergic patient, there are many variables involved in this technique which must be carefully weighed when interpreting test results. In the area of tobacco skin testing, such variables include: differences in antigenic content of the test extract, differences in route of administration, and heterogeneity of test groups.

ANTIGENIC PROPERTIES

Tobacco leaf contains a complex mixture of chemical components including: celluloses, starches, proteins, sugars, alkaloids, pectic substances, hydrocarbons, phenols, fatty acids, isoprenoids, sterols, and inorganic minerals (*69*). Theoretically, relatively few of these substances should be antigenic. Tobacco extracts of different composition result from differences in tobacco types and species, processing of tobacco, and preparation of the extract. Harkavy (*26*) has shown in some patients a differential skin reactivity to extracts from different types of tobacco. Coltoiu, et al. (*9*) reported that 13 different antigens capable of inducing precipitins in rabbits have been isolated from tobacco pollen. Chu, et al. (*7*) prepared aqueous extracts of five commercial tobacco products which stimulated antibody formation in rabbits. The antigens contained in the extracts included both proteins and polysaccharides and had molecular weights ranging from 20,000 to 60,000.

Silvette, et al. (*64*) reviewed several papers dealing with the immunology of nicotine and concluded that nicotine was nonantigenic. Harkavy (*25*), who performed some of the earliest studies on the antigenicity of nicotine, could not exclude the possibility that nicotine may act as a hapten. A hapten is a compound which, although not antigenic by itself, reacts with antibody and conveys antigenic specificity when combined with another compound.

With pyrolysis many of the tobacco constituents undergo reactions involving oxidation, dehydrogenation, cracking, rearrangement, and condensation (*69*). Many new compounds are formed. Pipes (*51*) demonstrated, through exhaustion of passive transfer reactivity in skin sites, that allergy to tobacco smoke in man is distinct from that of allergy to tobacco leaf. Tobacco smoke exhausted reactivity in sites injected with tobacco smoke sensitized serum; reactivity was reduced but not exhausted with tobacco extract. The converse was true with passive transfer sites of tobacco-sensitized serum; tobacco extracts abolished allergic reactivity whereas tobacco smoke extract produced a diminution but not total exhaustion. He concluded that it would be useful to test human subjects for both tobacco leaf and tobacco smoke sensitivity. Kreis, et al. (*39*) have speculated that tobacco leaf antigenicity may be lost with pyrolysis.

Coltoiu, et al. (*9*) recently emphasized the importance of removing all irritants from test extracts. In a clinical setting, allergy to tobacco additives such as menthol has also been suspected (*47*).

SKIN TESTING

Intracutaneous injection of test antigen is a widely used method of skin testing. Patch tests have also been used in cases of suspected contact dermatitis.

Rosen (*54*) has observed that skin testing does not accurately duplicate the most common route of exposure to tobacco, i.e., tobacco smoke inhalation. For those involved in the production of tobacco products, inhalation of tobacco dust or direct contact with tobacco may play important roles in sensitization (*9*).

The extensive literature on cutaneous sensitivity to tobacco extracts includes comparisons of the prevalence of positive skin reactions in different groups, such as "normal" nonsmoking adults (*17, 68*), "normal" smokers (*17, 33*), allergic patients (*59, 76*), children (*41, 50*), tobacco workers (*6, 9*), and patients with specific diseases, e.g., thromboangiitis obliterans (*28, 73*). Harkavy reported on tobacco skin reactions in several different groups of patients (*30*). Many of the apparently discordant results in some of these reports can be traced to failure to compare similar populations or to control for differences in the test antigen or in the method of testing.

Sulzberger (*66*) studied the different types of skin reactions produced by intracutaneous injection of denicotinized tobacco extract. Three types of positive skin responses were observed: eczematous reactions; immediate wheal-and-flare reactions; and late reactions, probably of the tuberculin type. The wheal-and-flare response has been by far the predominant type (*42*).

This immediate wheal-and-flare response is a specific immune reaction (*64*) largely mediated by IgE. Patterson (*48*) recently proposed a simplified model explaining the mechanism of action of the skin sensitizing antibody (SSA). "Subsequent to stimulation of the animal by antigen, SSA are produced by cells of the lymphoid system possibly located in the alimentary and respiratory tract. . . . The SSA so produced are secreted in such a way that they reach the circulation, where circulating cells, predominantly basophilic leukocytes, are sensitized by attachment of the SSA to the cell surface. In addition, the SSA also leave the vascular compartment and sensitize mediator-releasing cells in tissues. The tissue cells are primarily mast cells . . . The immediate-type allergic reaction occurs when antigen is introduced into the individual sensitized by SSA, either by transfer of antigenic molecules through the respiratory or alimentary mucosal surface or by injection into the skin or vascular system. The antigens reach the antibody on the surface of the mast cells and initiate the intracellular events that result in mediator release from the cells." The actions of these mediators include smooth muscle contraction, vasodilation, and increased capillary permeability which can produce such clinical pictures as hay fever, asthma, and generalized anaphylaxis.

Until recently, direct skin testing and the passive transfer test (Prausnitz-Küstner reaction) were the only methods of studying IgE mediated responses. In the passive transfer test, serum from an allergic patient is injected into the skin of a normal subject. After a suitable interval the antigen is injected into the prepared site and adjacent normal skin. In a positive response, cutaneous reactivity is transferred to the normal subject at the injection site. The absence of a positive response in nearby normal skin excludes nonspecific irritation as a cause of the response and shows that the normal subject is not himself allergic to the antigen.

Harkavy and Witebsky (*34*) found and selectively absorbed tobacco reagins in patients showing multiple sensitivities. This selective absorption documented the immunologic mechanism of the skin reaction. Passive transfer of the SSA was also reported by Peshkin and Landay (*50*) and by Lima and Rocha (*41*). Lowell (*43*) stated, "The individual possessing skin-sensitizing antibody to the tobacco extract may be regarded as unequivocally allergic to the extract. . . ." Despite the inability of Sulzberger and Feit (*67*) to demonstrate tobacco reagins in their skin test positive patients, several investigators have found them (*26, 50, 75*).

Harkavy (*23*) biopsied urticarial wheals after intradermal injection of tobacco extract and found a local eosinophilia. He felt that this helped confirm the allergic mechanism of the positive skin test. He also biopsied the site of a delayed skin reaction to tobacco and found an eczematous type of response.

The delayed type hypersensitivity reaction is manifested by induration and erythema developing within 24 to 48 hours after injection of antigen. The absence of response in the first 6 to 8 hours after exposure to antigen helps exclude an Arthus reaction, which is also a slowly evolving allergic response. Serum antibodies are not involved in the initiation of delayed type hypersensitivity; rather, the initial step is thought to involve interaction of antigen and specialized lymphocytes (*10, 11*). Contact dermatitis is thought to be very nearly a pure type, delayed hypersensitivity reaction (*10, 11*).

The foregoing discussion has highlighted the studies concerning cutaneous sensitivity to tobacco extracts. Despite the complexities and contradictions, numerous workers agree that tobacco extract (leaf or smoke) is antigenic and can sensitize (*2, 7, 9, 18, 26, 43, 50, 52, 64, 66, 76*). Silvette, et al. (*64*) concluded, "It is, indeed, beyond question that allergy to tobacco extracts, presumably atopic in nature, is an established fact. . . ."

Lowell (*43*) observed that, in most instances, skin reactivity to an extract of tobacco actually means the presence of allergy in some degree to something in the extract. Armen and Cohen (*2*), Harkavy and Perlman (*31*), and Popescu, et al. (*52*) observed that tobacco extract is weakly antigenic. Armen and Cohen (*2*) were able to sensitize rabbits to tobacco proteins only after absorbing the protein to aluminum hydroxide, which served as an adjuvant.

Even though a positive skin test to tobacco extract may be due to a specific allergic reaction, the interpretation of such a positive test in a given patient or group of patients poses problems, since sensitivity to a battery of antigens has been demonstrated in individuals who are entirely free from allergic symptoms upon exposure to the antigens. Rosen (*54*) stated that this lack of correlation between positive skin tests and clinical symptoms is greater for tobacco than for other antigens such as pollens, dusts, and feathers. He and others have emphasized that the skin test has value only when correlated with clinical evidence.

Analysis of skin test studies in nonsmokers (*64*) shows that approximately 15 percent of such "healthy" individuals give positive reactions to tobacco extracts. Some studies of smokers reporting a 30 percent or more prevalence of skin sensitivity to tobacco extract (*33, 43*) have considered patients with multiple sensitivities, including that to tobacco. Atopic individuals have been noted to have a greater prevalence of skin sensitivity to tobacco than nonatopics (*64*); hence, in some studies an excess of atopic patients may account for a substantial part of the elevated prevalence of tobacco skin sensitivity reported for smokers.

Several workers have sought to use the skin test as a screening device for indicating an unusual susceptibility to the adverse effects of tobacco. DeCrinis, et al. (*13*), Fontana (*17*), and Redisch (*53*) have reported that patients with positive skin tests to tobacco extracts were more likely to have an adverse vascular response to tobacco as indicated by a fall in peripheral skin temperature on smoking. More recent studies have shown that a decrease in skin temperature with smoking is a reproducible response to nicotine found in "normal" individuals and does not appear to be confined to a specific group of smokers (*1, 56, 70*).

ADDITIONAL IMMUNOLOGICAL EFFECTS

Additional evidence is available to support the view that tobacco induces immunologic changes in man and animals. Armen and

Cohen (*2*), Chu, et al. (*7*), Harkavy and Perlman (*31*), and Zussman (*76*) induced precipitin formation in animals sensitized to tobacco extract. Kreis, et al. (*39*) studied precipitation reactions in 651 hospitalized patients, many of whom were suffering from tuberculosis or lung cancer. A precipitation reaction between the patients' sera and a commercial tobacco extract was found in 62.5 percent of the patients. Chu, et al. (*7*), using the same antigens as those employed to stimulate precipitin formation in rabbits, found serum antibodies in 40 percent of a group of smokers which precipitated specificially with the tobacco antigens. Only 7 percent of a group of nonsmokers demonstrated these antibodies.

Savel (*59*) studied eight nonsmoking, allergic individuals who developed immediate upper respiratory discomfort after being exposed to cigarette smoke. As measured by the uptake of tritiated thymidine, the lymphocytes of these individuals were stimulated by cigarette smoke, while "normal" lymphocytes were depressed. The author stated that the correlation of this test with specific forms of clinical allergy remains uncertain.

Some investigators have observed abnormal laboratory test results in smokers as compared to nonsmokers, which may indicate an allergic response in the former group. Schoen and Pizer (*60*) described a smoking woman who demonstrated a striking blood eosinophilia while smoking cigarettes. Upon cessation of smoking, the eosinophil count returned promptly to normal levels. Resumption of smoking was associated with a return of the eosinophilia. Heiskell, et al. (*36*) found a significant increase in C-reactive protein and an abnormal seroflocculant for ethyl choledienate in smokers as compared to nonsmokers. Plasma histaminase levels were reported by Kameswaran, et al. (*38*) to be elevated in smokers.

Experimental animal sensitization to tobacco was reported by Friedlander, et al. (*19*) in male rats. Harkavy (*29*) confirmed these results in male rats and also obtained positive Schultz-Dale reactions in the sensitized animals; however, female rats failed to demonstrate this sensitization. Harkavy (*24*) reported cardiac histological abnormalities in three rabbits sensitized with denicotinized tobacco extracts. The abnormalities found in the three rabbits, respectively, included: intimal proliferation, focal fragmentation of the internal elastic membrane, and loss of smooth muscle fibers in the media of a branch of a coronary artery; focal intimal proliferation and fibrinoid alterations in the media of a small coronary vessel; and a focus of myocardial fibrosis and necrosis.

EFFECT ON THE IMMUNE RESPONSE

The effect of tobacco on the immune response has received some attention. Early studies in rabbits suggested that tobacco smoke retarded the production of agglutinins in rabbits immunized against typhoid (*14*).

A variety of observations indicate that ingestion of antigenic material by the macrophage may be an essential step in the immune response (*3*). Bruni (*5*) found that cigarette smoke suppressed phagocytosis in rabbits. Green and Carolin (*20*) performed *in vitro* studies in rabbit alveolar macrophages and observed that cigarette smoke inhibited the capacity of these cells to inactivate bacteria. Harris, et al. (*35*) reported no differences in the phagocytic ability of macrophages taken from human smokers and nonsmokers, but he also concluded that his data neither contradicted nor supported Green's work. Cohen and Cline (*8*), while noting that macrophages from smokers had normal phagocytic capacity, demonstrated suboptimal macrophage function in an environment of low O_2 tension, a state found more frequently in smokers than nonsmokers. Maxwell, et al. (*45*), using guinea pigs, found that smoke exerted no effect on phagocytosis; nevertheless, smoke seemed to impair the phagocytes' ability to inactivate bacteria. Nicotine has been shown by Meyer, et al. (*46*) to exert a depressant effect on sheep pulmonary alveolar macrophage respiration and ATPase activity. Recently, Yeager (*74*) reported that water soluble constituents of cigarette smoke depress protein-synthesis in rabbit alveolar macrophages *in vitro*.

Lewis, et al. (*40*) found that cigarette smoking had a suppressive action on secretory IgA production in normal subjects but not in subjects with chronic respiratory disorders. Vos-Brat and Rumke (*71*) recently reported that IgG serum concentrations and the response of lymphocytes to phytohemagglutinin were significantly lower in smokers than nonsmokers.

A number of investigators have reported increased rates of respiratory illnesses among cigarette smokers (*70*). Finklea, et al. (*16*) studied antibody response in 289 volunteers after the 1968 Hong Kong influenza epidemic. They reported a significant decrease among cigarette smokers in the persistence of hemagglutination inhibition antibody after natural infection or vaccination with A_2 antigens. They postulated that this antibody deficit among cigarette smokers might be related to increased illness during influenza outbreaks.

IRRITANT AND PHARMACOLOGIC EFFECTS

As Lowell (*43*) has emphasized, the pharmacologic, irritant, and allergic effects of tobacco are difficult to distinguish. Acrolein and acetaldehyde are potent irritants found in tobacco smoke, which, as demonstrated in animal studies, are capable of releasing chemical mediators such as histamine (*58*). The inhalation of tobacco smoke causes bronchial constriction, mucus hypersecretion, and ciliary stasis (*57*) in man, all of which can contribute to a clinical picture indistinguishable from an allergic reaction. Several authors (*44, 61, 63*) share Sherman's (*62*) view that "... tobacco smoke is an important secondary factor in precipitating allergic symptoms through its action as a nonspecific irritant."

Speer (*65*) recently compared the subjective responses of two groups of nonsmokers to tobacco smoke exposure. One group of 191 patients suffered from documented allergies. In one-sixth of these patients a positive skin test to tobacco extract was found, but only a few patients were seen with objective symptoms which could be traced to tobacco smoke. The other group of 250 patients had no history of allergy and was studied by questionnaire only. Eye irritation, nasal symptoms, headache, and cough were common in both groups. Speer concluded that these effects of tobacco smoke were irritative rather than allergic in origin. The data presented in this study demonstrate that tobacco smoke can contribute to the discomfort of many individuals; they do not rule out a possible contribution from allergic reactions.

Harkavy (*30*) cited experimental data distinguishing allergic effects from pharmacologic effects of smoking such as increased heart rate and decreased skin temperature.

Additional studies are needed to separate the pharmacologic, irritant, and allergic effects of tobacco smoke.

CLINICAL ALLERGY

It is important to understand what role tobacco and tobacco smoke may play in clinical allergy because many individuals are exposed to them in varying concentrations throughout the year.

A variety of conditions have been ascribed to allergic manifestations toward tobacco leaf or smoke including: asthma, rhinitis, urticaria, angioneurotic edema (giant hives), contact dermatitis, migraine headache, gastrointestinal symptoms, and various cardiovascular disturbances (*64*); however, some case reports are lacking in documentation (*4, 49*). A small group of patients having cutaneous sensitivity to tobacco and showing complete disappearance of symptoms when free from exposure to tobacco were reported by Rosen and Levy (*55*). Included in this group were cases of asthma and urticaria.

Studies of atopic individuals have revealed a group of nonsmoking patients with cutaneous sensitivity to tobacco who developed clinical symptoms upon exposure to tobacco smoke (*59, 76*). In none of these studies (*54, 59, 76*) have detailed immunologic investigations, attempting to link clinical and immunologic events, been performed.

Lowell (*43*) reviewed case reports of contact dermatitis to tobacco among tobacco workers and noted that because of "...the small proportion of exposed individuals who develop such lesions, and the tendency for it to clear completely when contact with tobacco is avoided and to return on reexposure, an allergic cause in certain instances would appear to be highly probable." Recently, case reports have appeared identifying tobacco smoke and tobacco smoke residue as causes of contact dermatitis (*6, 12, 72*).

Harkavy's (*28*) early reports of a greater number of reactors to tobacco extract among patients with thromboangiitis obliterans (TAO) than among controls drew attention to the cardiovascular system as a possible "susceptible" organ for allergic reactions (*15*). Harkavy continues to be a strong proponent of the role of tobacco allergy in a wide range of cardiovascular abnormalities, including coronary artery disease (*21, 22, 25, 27, 31, 32*). This view on tobacco allergy as one of the etiological factors in coronary heart disease (CHD) has not received much attention.

Silvette, et al. (*64*) reviewed reports (*28, 33, 66, 68, 73*) on the prevalence of skin sensitivity in patients with TAO as compared to controls and cited possible reasons for a higher prevalence of positive skin tests to tobacco in these patients.

In general, the evidence relating TAO to tobacco allergy is inconclusive.

SUMMARY

1. Tobacco leaf, tobacco pollen, and tobacco smoke are antigenic in man and animals.
2. (a) Skin sensitizing antibodies specific for tobacco antigens have been found frequently in smokers and nonsmokers. They appear to occur more often in allergic individuals. Precipitating antibodies specific for tobacco antigens have also been found in both smokers and nonsmokers.
   (b) A delayed type of hypersensitivity to tobacco has been demonstrated in man.
   (c) Tobacco may exert an adverse effect on protective mechanisms of the immune system in man and animals.
3. (a) Tobacco smoke can contribute to the discomfort of many individuals. It exerts complex pharmacologic, irritative, and allergic effects, the clinical manifestations of which may be indistinguishable from one another.
   (b) Exposure to tobacco smoke may produce exacerbation of allergic symptoms in nonsmokers who are suffering from allergies of diverse causes.
4. Little is known about the pathogenesis of tobacco allergy and its possible relationship to other smoking-related diseases.

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CHAPTER 8

Public Exposure to Air Pollution From Tobacco Smoke

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PUBLIC EXPOSURE TO AIR POLLUTION FROM TOBACCO SMOKE

The purpose of this chapter is to summarize the present state of evidence concerning the effects of exposure to an atmosphere containing either tobacco smoke or its constituents. Since the identification of cigarette smoking as a serious health hazard to the smoker was based on clinical and epidemiological observations that nonsmokers have much lower mortality and morbidity rates from a number of conditions, it is obvious that cigarette smoking is normally a greater hazard to the smoker than is the typical level of exposure to air pollutants produced by the smoking of cigarettes which many nonsmokers experience. This would be consistent with the voluminous data which show a dose-response relationship between the level of exposure to smoke and the magnitude of its effect.

The research so far reported on the nature and effects of exposure to smoke-pollutants in the atmosphere has not been as extensive and well-controlled as that done on the health effects of smoking on the smoker himself. Knowledge on this subject can be separated into four major areas of concern:

1. The extent to which the components of cigarette smoke contaminate the atmosphere and are absorbed by the nonsmoker.
2. The effects of low levels of carbon monoxide on human health.
3. Allergic, adverse, and irritative reactions to cigarette smoke among nonsmokers.
4. The known harmful effects of the passive inhalation of cigarette smoke in animals.

THE EXTENT TO WHICH THE COMPONENTS OF CIGARETTE SMOKE CONTAMINATE THE ATMOSPHERE AND ARE ABSORBED BY THE NONSMOKER

Theoretical models of this contamination have been constructed. Owens and Rossano (*44*) have noted that most popular cigarettes release into the atmosphere approximately 70 mg. of dry particulate matter (about 60 mg. in the sidestream and slightly over 20 mg. in the mainstream, about one-half of the latter being absorbed by the smoker and one-half expelled into the ambient air) and 23 mg. carbon monoxide per cigarette. This material adds to the cleaning problem of the air of any enclosed space and contributes to residual odors. In a recent study of particulate matter filtration in domestic premises (*35*), the authors observed that the smoking of one cigar completely overcame the effect of an electrostatic filtration device for one hour.

Atmospheric pollutants caused by smoking are derived from two major sources: mainstream and sidestream smoke. Mainstream smoke emerges from the tobacco product through the mouthpiece during puffing, whereas sidestream smoke comes from the burning cone and from the mouthpiece during puff intermissions (*60*). The tobacco smoke released into the atmosphere consists of all the sidestream smoke as well as that part of the mainstream smoke which has been either held in the smoker's mouth or taken into his lungs and then expelled. The actual amount of material to which individuals are exposed in the presence of smokers depends upon the amount of smoke produced, the depth of inhalation on the part of the smoker, the ventilation available for the removal or dispersion of the smoke, and the proximity of the individual to the smoker. The length of time of exposure to those pollutants is extremely important in determining how much is absorbed into the body. The pattern of smoking influences the amount produced by altering the content of the exhaled smoke. As shown by Dalhamn, et al. (*10, 11*), mouth absorption removes approximately 60 percent of the water-soluble volatile components (e.g., acetaldehyde), 20 percent of the nonwater-soluble volatile components (e.g., isoprene), 16 percent of the particulate matter, and only three percent of the carbon monoxide. Thus, the smoker who does not inhale "filters" a portion of the smoke components in his mouth before expelling them into the ambient air. On the other hand, the lungs retain from 86 to 99 percent of the volatile and particulate substances and approximately 54 percent of the carbon monoxide inhaled. Hence, the inhaling smoker "filters" the mainstream smoke rather effectively before expelling it into the ambient air. A factor which has apparently not been investigated is the difference in the smokers' "filtration" of mainstream smoke when the smoke is exhaled through the nose instead of the mouth.

Thus, the nonsmoker breathes smoke-containing air composed of sidestream smoke and mainstream smoke exhaled by smokers. The inhaling smoker receives nearly the full amount of mainstream smoke as well as a portion of sidestream smoke and smoke exhaled by himself and other smokers. The smoker who does not inhale receives those compounds which are absorbed from the mainstream smoke in his mouth, as well as absorbing the sidestream smoke and the smoke exhaled by himself and other smokers contained in the air he breathes.

Since pipe and cigar smokers inhale less commonly than do cigarette smokers, their contribution to the substances in the air breathed in exposure to smoke pollutants consists of a composite of sidestream smoke and relatively unfiltered mainstream smoke which has been held in the mouth and then expelled.

The actual effluents in the mainstream and sidestream cigarette smoke have been considered by Pascasio, et al. (*45*) and Scassellati Sforzolini and colleagues (*50, 51*). These authors stated that "tar" and nicotine levels in sidestream smoke may be significantly higher than those of mainstream smoke and may be harmful to the nonsmoker. Actual volume measurements were not reported, however.

Actual measurements of the contamination due to cigarette smoking have been carried out by a number of research groups. A recent, well-controlled study by Harke (*24*) involved the smoking of 42 cigarettes in 16 to 18 minutes using German blend cigarettes of 85 mm. length, 18 mm. filter, and smoked to a 25 mm. butt length in a room with a volume of 57 cubic meters (approximately the equivalent of a room with a 10-foot ceiling and dimensions of 12 by 14 feet). The author observed that in the absence of ventilation the atmosphere contained up to 50 p.p.m. carbon monoxide and .57 mg./m.^{3} nicotine. With substantial ventilation, these levels fell significantly (to approximately 10 p.p.m. carbon monoxide and .10 mg./m.^{3} nicotine). He also found that cigar smoke (9 cigars of Clear Sumatra tobacco smoked in 30 to 35 minutes) produced similar amounts of contamination while pipe smoke (3 grams of Navy type medium cut tobacco smoked as eight pipefuls in 35 to 40 minutes) produced much less. Other authors have made similar measurements. Galuskinova (*20*) found that 3,4-benzpyrene levels in a smoky restaurant were from 2.82 to 14.4 mg./100 m.^{3} as compared to outside atmospheric levels of 0.28 to 0.46 mg./100 m.^{3}, although burning of food particles may have contributed to the presence of 3,4-benzpyrene in this setting. Kotin and Falk (*33*) have shown that sidestream cigarette smoke condensate may contain more than three times as much benzo(a)pyrene as mainstream smoke. Srch (*55*) observed that the smoking of 10 cigarettes to a 5 mm. butt length in an enclosed car of 2.09 m.^{3} volume produced carbon monoxide levels up to 90 p.p.m. Lawther and Commins (*34*), working with a ventilated chamber, found levels of up to 20 p.p.m. of carbon monoxide after seven cigarettes were smoked in one hour; however, peaks of up to 90 p.p.m. were recorded at the seat next to the smoker. Coburn, et al. (*9*) recorded levels of 20 p.p.m. of carbon monoxide in a small conference room after 10 cigarettes were "burned." Harmsen and Effenberger (*25*) reported up to 80 p.p.m. of carbon monoxide in an enclosed 98 m.^{3} room (approximately the equivalent of a room with a 10-foot ceiling and dimensions of 18 by 20 feet) in which 62 cigarettes had been smoked in two hours.

TABLE 1.—*Percent of COHb during and following exposure to 50 p.p.m. of CO.*

Time during exposure	Mean	Range	Number of subjects
Preexposure	0.7	0.4–1.5	11
30 minutes	1.3	1.3	3
1 hour	2.1	1.9–2.7	11
3 hours	3.8	3.6–4.2	10
6 hours	5.1	4.9–5.5	5
8 hours	5.9	5.4–6.2	5
12 hours	7.0	6.5–7.9	3
15 ½ hours	7.6	7.2–8.2	3
22 hours	8.5	8.1–8.7	3
24 hours	7.9	7.6–8.2	3
Time without exposure after 1 hour of exposure			
30 minutes	1.8	1.8	3
1 hour	1.7	1.6–1.8	3
2 hours	1.5	1.4–1.5	3
5 hours	1.1	1.0–1.1	2
Time without exposure after 3 hours of exposure			
30 minutes	3.7	3.4–3.9	3
1 hour	3.3	2.7–3.8	3
2 hours	2.7	2.3–3.0	3
Time without exposure after 8 hours of exposure			
30 minutes	5.6	5.1–5.9	3
1 hour	5.1	4.8–5.4	3
1 ¾ hours	4.0	—	—
11 hours	1.5	1.4–1.7	3
Time without exposure after 24 hours of exposure			
30 minutes	7.5	7.2–7.8	3
1 hour	6.7	6.4–7.1	3
2 hours	5.8	5.6–6.2	3

SOURCE: Stewart, et al. (56).

Another set of contaminants probably present in a tobacco smoke-polluted atmosphere are the oxides of nitrogen. These, specificially NO and NO_2, have been shown to be present in tobacco smoke although the type most likely to be present in the atmosphere is NO_2. No measurements have been reported of the amount of NO_2 in smoke-filled rooms. The importance of obtaining and evaluating this information is stressed by the results of Freeman and Haydon and their colleagues (*17, 18, 19, 27, 28*) and of Blair, et al. (*5*) who observed bronchial and pulmonary parenchymal lesions in rodents continuously exposed to low levels of NO_2.

Other experimenters have measured carboxyhemoglobin (COHb) levels in nonsmokers exposed to cigarette smoke pollutants. Srch (*55*) observed that the COHb level in two nonsmokers rose from 2 to 5 percent (that of smokers from 5 to 10 percent) when seated in the cigarette-smoke contaminated car mentioned above (exposure to 90 p.p.m.). Harke (*24*) reported that when seven nonsmokers were exposed for approximately 90 minutes to a "smoked" room containing 30 p.p.m. of CO there was a rise in COHb from a mean of 0.9 percent to 2.0 percent. In 11 smokers subjected to the same conditions, COHb rose from a mean of 3.3 percent to 7.5 percent. With improved ventilation of the experimental room, the COHb level decreased significantly.

The CO exposures and COHb levels reported above closely approximate the results obtained following experimental chamber exposure of humans to various levels of CO. The uptake of CO by the person depends on, among other parameters: CO concentration, previous COHb level, the level of activity, and the person's state of health. Equilibrium between CO concentration in the lung and in the blood requires over 12 hours exposure. However, as may be noted in table 1, reproduced from Stewart, et al. (*56*) and derived from measures of COHb in young sedentary males who were not smoking, over half of the equilibrium COHb level is reached within three to four hours of the onset of exposure. The equilibrium value associated with 100 p.p.m. is approximately 14 to 15 percent COHb. Exposure to 100 p.p.m. in the nonsmoker can lead to 3.0 percent of COHb within 60 minutes and 6.0 percent in two hours (*16*). Of equal significance is that COHb has a half-life of at least three to four hours in the body. As shown in table 1, the COHb level fell only to 2.7 percent in the two hours following cessation of exposure to 50 p.p.m. from the end exposure level of 3.7 percent. This lengthy half-life extends the period of effect of exposure to CO and provides for a buildup of COHb concentration from fresh exposures.

THE EFFECTS OF LOW LEVELS OF CARBON MONOXIDE ON HUMAN HEALTH

The data on the effect of low levels of carbon monoxide on human psychological and physiological function have been summarized in two recent publications (*8, 58*).

There is presently much discussion as to the physiologic and psychophysiologic effects of exposure to levels of CO approximating 50 to 100 p.p.m. Beard and Grandstaff (*4*) observed that exposure to 50 p.p.m. of CO for from 27 to 90 minutes altered auditory discrimination, visual acuity, and the ability to distinguish relative brightness. McFarland (*40*) observed that COHb levels of 4 to 5 percent caused visual threshold impairment. Ray and Rockwell (*48*), reporting on a study of the driving ability of three subjects under varying CO exposure, observed that the presence of 10 percent COHb was associated with increased response time for taillight discrimination and increased variance in distance estimation. Schulte (*52*) observed that increased errors in cognitive and choice discrimination tests were manifest at levels of COHb as low as 3 percent. Chevalier, et al. (*7*) have also observed that levels of 4 percent COHb in nonsmokers are associated with an increase in oxygen debt formation with exercise similar to that seen in smokers.

On the other hand, other investigators utilizing complex psychomotor tasks in men and monkeys have observed no decrement in function upon exposures to CO at 50 to 250 p.p.m. (*2, 3, 23, 41, 56*).

Animals exposed to low levels of CO (50 to 100 p.p.m.) continuously for weeks have shown varying degrees of cardiac and cerebral damage similar to that produced by hypoxia (*21, 47, 57*).

Finally, the possible effects of exposure to 50–100 p.p.m. CO on patients with coronary heart disease (CHD) were investigated by Ayres, et al. (*1*) who observed a decrease in arterial and mixed venous oxygen tensions with COHb saturations of 5 percent. Certain patients with CHD developed altered lactate and pyruvate metabolism with COHb levels of 5 to 10 percent suggesting myocardial hypoxia.

The evidence concerning the effect of low levels of carbon monoxide has recently been reviewed and evaluated by the National Air Quality Criteria Committee of the National Air Pollution Control Administration (*58*). The following is taken from the published conclusions of the Advisory Committee (also see table 2):

> "Experimental exposure of nonsmokers to 58 mg/m^3 (50 ppm) for 90 minutes has been associated with impairment in time-interval discrimination.... This exposure will produce an increase of about 2 percent COHb in the blood. This same increase in blood COHb will occur with continuous exposure to 12 to 17 mg/m^3 (10 to 15 ppm) for 8 or more hours....
>
> "Experimental exposure to CO concentrations sufficient to produce blood COHb levels of about 5 percent (a level producible by exposure to about 35 mg/m^3 for 8 or more hours) has provided in some instances evidence of impaired performance on certain other psychomotor tests, and an impairment in visual discrimination....
>
> "Experimental exposure to CO concentrations sufficient to produce blood COHb levels above 5 percent (a level producible

TABLE 2.—*Effects of carbon monoxide.*

Environmental conditions	Effect	Comment
58 mg./m.^{3} (50 p.p.m.) for 90 minutes	Impairment of time-interval discrimination in non-smokers.	Blood COHb levels not available, but anticipated to be about 2.5 percent. Similar blood COHb levels expected from exposure to 10 to 17 mg./m.^{3} (10 to 15 p.p.m.) for 8 or more hours.
115 mg./m.^{3} (100 p.p.m.) intermittently through a facial mask	Impairment in performance of some psychomotor tests at a COHb level of 5 percent.	Similar results may have been observed at lower COHb levels, but blood measurements were not accurate.
High concentrations of CO were administered for 30 to 120 seconds, and then 10 minutes was allowed for washout of alveolar CO before blood COHb was measured.	Exposure sufficient to produce blood COHb levels above 5 percent has been shown to place a physiologic stress on patients with heart disease.	Data rely on COHb levels produced rapidly after short exposure to high levels of CO; this is not necessarily comparable to exposure over a longer time period or under equilibrium conditions.

SOURCE: Adapted from U.S. Public Health Service, Air Quality Criteria for Carbon Monoxide. Washington, D.C., U.S. Department of Health, Education, and Welfare (58).

> by exposure to 35 mg/m^3 or more for 8 or more hours) has provided evidence of physiologic stress in patients with heart disease. . . ."

The levels of carbon monoxide found to be present in "smoked" rooms (20 to 80 p.p.m.) are similar to the levels (30 to 50 p.p.m.) which the Advisory Committee has concluded are associated with adverse health effects:

> "An exposure of 8 or more hours to a carbon monoxide concentration of 12 to 17 mg/m^3 (10 to 15 ppm) will produce a blood carboxyhemoglobin level of 2.0 to 2.5 percent in nonsmokers. This level of blood carboxyhemoglobin has been associated with adverse health effects as manifested by impaired time interval discrimination. Evidence also indicates that an exposure of 8 or more hours to a CO concentration of 35 mg/m^3 (30 ppm) will produce blood carboxyhemoglobin levels of about 5 percent in nonsmokers. Adverse health effects as manifested by impaired performance on certain other psychomotor

tests have been associated with this blood carboxyhemoglobin level, and above this level there is evidence of physiologic stress in patients with heart disease."

These levels of CO are also similar to that set as the time-weighted occupational Threshold Limit Value of 50 p.p.m. for a 40-hour week (five 8-hour days) which has been in effect in the United States for the past several years (*13*). A further reduction in this limit to 25 p.p.m. is now under consideration. These levels of CO exceed those recently set by the Environmental Protection Agency as the national primary and secondary ambient air quality standards for CO (*14*). These standards are:

(a) 10 milligrams per cubic meter (9 p.p.m.)—maximum 8-hours concentration not to be exceeded more than once per year.

(b) 40 milligrams per cubic meter (35 p.p.m.)—maximum 1-hour concentration not to be exceeded more than once per year.

ALLERGIC AND IRRITATIVE REACTIONS TO CIGARETTE SMOKE AMONG NONSMOKERS

(A more detailed discussion of this subject is presented in the Allergy chapter of this report.)

Several investigators have reported on the discomfort and symptoms experienced by both allergic and nonallergic individuals upon exposure to tobacco smoke. Johansson and Ronge (*31, 32*) in 1965 and 1966 have observed that the acute irritation experienced by nonsmokers in the presence of tobacco smoke is maximal in warm, dry air and that nonsmokers experience more nasal irritation than ocular irritation as compared with smokers exposed to similar amounts of smoke in the atmosphere. Speer (*54*) studied the reactions of 441 nonsmokers divided into two groups, one composed of individuals with a history of allergic reactions and the other of individuals without such a history. The allergic group underwent skin testing for the presence of sensitivity to tobacco extract while the "nonallergic" group was determined solely by questionnaire concerning subjective allergic responses. Approximately 70 percent of both groups experienced eye irritation while other symptoms differed in their frequency from group to group (nasal symptoms: allergic 67 percent, "nonallergic" 29 percent; headache: allergic 46 percent, "nonallergic" 31 percent; cough: allergic 46 percent, "nonallergic" 25 percent; and wheezing: allergic 22 percent, "nonallergic" 4 percent). Thus, a significant proportion of nonsmoking individuals report discomfort and respiratory symptoms on exposure to tobacco smoke.

Other authors have attempted to separate out those patients who may have specific allergies to smoke. Zussman (*61*) found that in a random series of 200 atopic patients 16 percent were clinically sensitive to tobacco smoke, and that a majority of these were aided by desensitization therapy. In an earlier study, Pipes (*46*) observed that 13 percent of 229 patients with respiratory allergy showed positive skin tests to tobacco smoke. Savel (*49*) has recently reported on eight nonsmokers observed to be clinically hypersensitive to tobacco smoke. After *in vitro* incubation of their lymphocytes with cigarette smoke, increased incorporation of tritiated thymidine was recorded; similar exposure of the lymphocytes of those not sensitive resulted in depression of tritiated thymidine uptake.

Luquette, et al. (*39*) have recently reported on the immediate effects of exposure to cigarette smoke in school-age children. They observed that heart rate and blood pressure rose with such exposure, although questions remain about the adequacy of their controls and the manner in which the experimental situation may have excited the subjects. Finally, Cameron, et al. (*6*) observed that acute respiratory illnesses were more frequent among children from homes in which the parents smoked than among children of nonsmoking parents. The meaning of these results is uncertain since smoking by the children was not considered and the level of exposure to cigarette smoke in their homes was not measured. Shy, et al. (*53*) in a study of second grade Chattanooga school children failed to demonstrate a relationship between parental smoking habits and the respiratory illness rates of their children.

THE KNOWN HARMFUL EFFECTS OF THE PASSIVE INHALATION OF CIGARETTE SMOKE IN ANIMALS

A number of investigators have studied the effects of the passive inhalation of high concentrations of cigarette smoke on the pulmonary parenchyma and tracheobronchial tree of animals. The results of these investigations are listed in detail in the recent report to Congress, "The Health Consequences of Smoking," (*59*) in table 9 of the Bronchopulmonary chapter, and table 16 of the Cancer chapter.

The pathologic changes observed in the respiratory tract of the animals included parenchymal disruption, bronchitis, tracheobronchial epithelial dysplasia and metaplasia, and pulmonary adenomatous tumor formation. Leuchtenberger, et al. (*36*) exposed 151 mice to the smoke of from 25 to 1,526 cigarettes over a period of 1 to 23 months and observed that 20 percent of the animals developed severe bronchitis with atypism. Working with 30 control rabbits exposed to up to 20 cigarettes per day for two to five years, Holland, et al. (*30*) observed increased focal and generalized hyperplasia of the bronchial epithelium and generalized emphysema in the exposed rabbits. Hernandez, et al. (*29*) observed significantly more pulmonary parenchymal disruption in adult greyhound dogs exposed to cigarette smoke 10 times per week for approximately one year than in nonexposed control animals.

Lorenz, et al. (*38*) observed no increase in respiratory tract tumor formation above that seen in controls in 97 Strain A mice exposed to cigarette smoke for up to 693 hours. Essenberg (*15*), however, exposed Strain A mice to cigarette smoke for 12 hours a day for up to one year and observed significantly more papillary adenocarcinomas in the exposed than in the control group. An increased percentage of hybrid mice were found by Mühlbock (*42*) to have alveolar carcinomas among the experimental group exposed to smoke for two hours a day for up to 684 days when compared with a nonexposed group. Similarly, Guerin (*22*) observed that 5.1 percent of rats exposed to cigarette smoke for 45 minutes a day for two to six months showed pulmonary tumors compared to 2.4 percent of the control mice.

Leuchtenberger, et al. (*37*), working with 400 female CF_1 mice, observed only a slight increase in the presence of pulmonary adenomatous tumors among those exposed to cigarette smoke compared with those in the control group. The authors commented that the presence of tumors showed an age relationship independent of smoking exposure. Otto (*43*) found that 11 percent of a group of albino mice exposed to 12 cigarettes a day for up to 24 months showed pulmonary adenomas as compared with five percent of the control non-exposed group. Dontenwill and Wiebecke (*12*) found that increasing the exposure of golden hamsters to up to four cigarettes a day for up to two years was associated with an increasing percentage of animals showing desquamative metaplasia and bronchial papillary metaplasia. Harris and Negroni (*26*) exposed 200 C57BL mice to cigarette smoke for 20 minutes a day every other day for life and found eight adenocarcinomas as compared to none in the control group.

Because the damage observed in these experiments was seen after prolonged exposure to high concentrations of cigarette smoke, and because the comparability of animal exposure to smoke with that of human exposure in smoke-filled rooms is unknown, it is presently impossible to be certain from animal experimentation about the extent of the damage that may occur during long-term intermittent exposure to lower concentrations.

SUMMARY

1. An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals.

2. The level of carbon monoxide attained in experiments using rooms filled with tobacco smoke has been shown to equal, and at times to exceed, the legal limits for maximum air pollution permitted for ambient air quality in several localities and can also exceed the occupational Threshold Limit Value for a normal work period presently in effect for the United States as a whole. The presence of such levels indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease and coronary heart disease.

3. Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various concentrations to adversely affect animal pulmonary and cardiac structure and function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known.

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CHAPTER 9

Harmful Constituents of Cigarette Smoke

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HARMFUL CONSTITUENTS OF CIGARETTE SMOKE[*]

Cigarette smoke contains a large number and a wide variety of compounds which may result in complex and multiple pathophysiological effects on various tissues and organ systems. Although the constituents of cigarette smoke are usually divided for convenience into the two categories of particulate and gas phases,[**] many of them exist in a distribution equilibrium, that is, they are present partially in the gas phase and partially in the particulate phase. This review concerns itself with judgments concerning the harmful constituents of cigarette smoke whether these are found primarily in the gas phase or in the particulate phase.

Constituents of cigarette smoke may enter the body by a variety of routes. Theoretically, the route of entry and subsequent absorption could affect the degree to which various organs are subjected to specific cigarette smoke constituents. Some constituents, particularly the water soluble components of the gas phase, may be absorbed by the nasal and oropharyngeal mucous membranes, or may be dissolved in the saliva and swallowed, thus allowing for possible gastric or intestinal absorption. Other constituents are absorbed along the tracheobronchial tree, and the distance which they reach before being absorbed or deposited depends on such factors as the depth of inhalation and the particle size. The absorption of gases in the tracheobronchial tree appears to be in part dependent on the adsorption of gases to particulate matter. Another factor affecting the route and degree of absorption is the adequacy of pulmonary clearance by which constituents deposited or dissolved in the mucous sheath are delivered to the pharynx and then usually swallowed.

Of the hundreds of compounds identified in cigarette smoke, some occur in the smoke in concentrations which may be considered sufficient to present hazards to health. Other compounds appear in borderline concentrations. Still others, although potentially harmful, are probably not present in sufficient concentrations to contribute to the hazard, and some may be hazardous only when they interact with other substances in the smoke.

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[*] This report attempts to summarize the areas of general consensus reached in a special one-day conference of experts in this field which met in June 1970. This is not to imply that there was unanimous agreement on all statements contained herein. A list of participants in the meeting appears in the Acknowledgments.

[**] It should be noted that there is, at present, no available instrumentation permitting the separation and individual collection of the particulate and gas phases which duplicates the precise physicochemical conditions prevailing in cigarette smoke as it is inhaled. A widely accepted arbitrary distinction between the two phases is as follows: If 50 percent or more of a given constituent is retained on a Cambridge filter (CM-113) during standardized machine smoking of a cigarette, then the compound is considered to belong to the particulate phase; if on the other hand more than 50 percent of the compound passes through the Cambridge filter under these conditions, then the constituent is considered to belong to the gas phase.

Substances and classes of substances in cigarette smoke which have been judged to contribute to the hazard of cigarette smoking have been classified into three priority groups. Those compounds which are judged most likely to contribute to the health hazards of smoking are listed in table 1. Additional substances which probably contribute to the health hazards of smoking are listed in table 2. Those compounds which are suspected contributors to the health hazards of smoking in the concentrations in which they are present in tobacco smoke are listed in table 3. Many other constituents of tobacco smoke are considered to be toxic under some conditions but probably do not present a health hazard in the concentrations in which they are generally found in cigarette smoke; these are not listed. This listing is not presented as final, and may be subject to modification as more information becomes available.*

In 1966, the Public Health Service prepared a technical report on "tar" and nicotine *(60)*. Tobacco "tar" is the name given to the aggregate of particulate matter in cigarette smoke after subtracting nicotine and moisture. In that report it was stated:

> "It is clear that the overall risk associated with cigarette smoking increases as the average number of cigarettes consumed per day increases. In the studies which have reported other measures of exposure such as pack-years, degree of inhalation, and maximum level of cigarette consumption, the same type of relationship holds."

Individuals may differ in their inherent susceptibility to diseases in which cigarette smoking plays a role and differ in their exposure to other factors which may increase the likelihood of these diseases. Within these groups of varying risk, the degree of exposure to cigarette smoke appears to be the most critical factor for the development of smoking related disease. Therefore, the general statement that the lower the dosage the lower the risk is the most useful guide available. It was also stated that:

> "It is possible for a cigarette to be altered in such a way that its 'tar' and nicotine content is reduced but certain other harmful effects, for example the effect of the gaseous phase, may be increased. Although this is a theoretical possibility,

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* Subsequent to the conference on which this report was based, several studies were published reporting the presence of N-nitrosamines in cigarette smoke. Since these substances are accepted as carcinogens in experimental animals, they represent another portion of the "tar" which probably contributes to the total health hazard (18, 24).

there is no evidence that this has occurred to any serious degree."

The consensus is that there is inadequate evidence to support a change in that view at the present time.

In addition, it was concluded that "the preponderance of scientific evidence strongly suggests that the lower the 'tar' and nicotine content of cigarette smoke, the less harmful would be the effect." Several studies reported since that time have added strong support to this position. The present review is an attempt to identify those constituents of the "tar" as well as those constituents considered part of the gas phase which are most likely to contribute to the health hazards from cigarette smoking.

TABLE 1.—*Compounds in cigarette smoke judged most likely to contribute to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Carbon Monoxide	5,240–21,400	G	(1, 10, 23, 26, 29, 34, 35, 37, 42, 46, 49, 61, 63)
Nicotine	200–2,400	P	(9)
[1] "Tar"	3,000–33,000	P	(9)

[1] "Tar" is defined as the total particulate matter collected by a Cambridge filter (CM-113) after subtracting moisture and nicotine and includes the class of compounds known as polycyclic aromatic hydrocarbons (PAH). PAH are generally accepted as being responsible for a substantial portion of the carcinogenic activity of the total "tar." Although "tar" from different cigarettes varies in its carcinogenic potential as measured by the bioassay methods in current use, it remains the most practical single "indicator" of total carcinogenic potential. Special mention should be made of Beta Naphthylamine which is a known human urinary bladder carcinogen for which there is no known safe level of exposure and which has been reported present in tobacco smoke in very low concentrations (16, 28, 30) (0.022 μgm./cigarette).

It is recognized that the substances in cigarette smoke may interact so that the combined pathological effects of several substances may be quite different from the sum of their effects produced in isolation. An example of this type of interaction might be the carcinogenic effects of tobacco "tar" as a result of the combined action of cancer initiating, cancer promoting, and cancer accelerating agents in producing the total effect. Such interactions theoretically could take place among substances within the gas phase, or substances within the particulate phase, or between constituents of the gas phase and constituents of the particulate phase. In the absence of data which identify the interactions of cigarette smoke components, judgments concerning the action or identification of harmful substances in cigarette smoke have, of necessity, been made pri-

Table 2.—*Compounds in cigarette smoke judged as probable contributors to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Acrolein	45–140	G	(12, 20, 21, 27, 36, 43, 45)
Cresol (all isomers)	68–97	P	(20, 40)
Hydrocyanic Acid	100–400	G	(26, 38, 43, 45, 46, 49, 53)
Nitric Oxide	0–600	G	(1, 3, 15, 40, 42, 44, 57)
Nitrogen Dioxide	0–10	G	(1, 40, 44, 57)
Phenol	9–202	P	(7, 19, 20, 32, 50, 52)

marily on the basis of the action of the individual substances. Nevertheless, experimental evaluation of modified cigarette smoke should be designed to take into account the possibility of such interaction.

Until there is a better understanding of the relative importance of the interaction of the constituents of cigarette smoke in the development of the diseases associated with cigarette smoking, it will be difficult to assess the significance of the reduction or elimination of one or several of the constituents named in this report. However, it is reasonable to take the position that unless there is positive information to the contrary, cigarettes in which overall "tar" and nicotine levels have been reduced present to the smoker lower concentrations of the harmful substances in the particulate phase. If, at the same time, significant reductions are made in those gas phase constituents which also contribute to the hazards of smoking, the resulting product should be less hazardous to health.*

The consensus is that a progressive and simultaneous reduction of all substances considered likely to be involved in the health hazards of smoking should be encouraged as the most promising step available at the present time towards the development of a less hazardous cigarette. Primary emphasis should be given to the reduction of the three substances or classes of substances named in the first table, and as a second priority to the reduction of those substances or classes of substances in the second table before reducing

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* An alternative point of view held by some is that smoking behavior is a response to the need to reach a certain nicotine level and that lowering the amount of nicotine available from a cigarette may result in an increase in the number of cigarettes smoked, the depth of inhalation, or the number of puffs in order to maintain an accustomed level. Such an increase in smoking might result in an increased inhalation of other hazardous substances in the smoke, thereby potentially negating the effect of reducing the amount available in each cigarette.

TABLE 3.—*Compounds in cigarette smoke judged as suspected contributors to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Acetaldehyde	180–1,440	G	(4, 21, 27, 36, 43, 45, 48, 49, 53, 59)
Acetone	88–650	G	(12, 21, 27, 36, 43, 45, 48, 49, 53)
Acetonitrile	140–200	G	(12, 43)
Acrylonitrile	10–15	G	(12, 43)
Ammonia	60–330	G	(2, 22, 40, 41, 43, 64)
Benzene	12–100	G	(11, 12, 25, 43, 45, 49, 53)
2,3–Butadione	43–200	G	(43, 46, 49, 53)
Butylamine	3	P	(31, 40, 41)
[1] Carbon Dioxide	23,100–78,300	G	(1, 10, 15, 23, 26, 29, 34, 35, 42, 46, 49, 63)
Crotononitrile	4	G	(43)
Dimethylamine	10–11	P	(31, 40, 41)
DDT	0–0.77	P	(17, 39, 54)
Endrin	0.06	P	(14)
Ethylamine	10–11	G	(22, 31, 40, 41)
Formaldehyde	20–41	G	(4, 36, 43, 48, 53)
Furfural	45–110	P	(4, 13, 36)
Hydrogen Sulphide	12–35	G	(10, 43, 51, 58)
Hydroquinone	83	P	(6, 7)
Methacrolein	9–11	G	(12, 43)
Methyl Alcohol	90–300	G	(12, 21, 43, 46, 49)
Methylamine	20–22	G	(22, 31, 40, 41)
Nickel compounds	0–0.58	P	(5, 8, 47, 55, 56)
Pyridine	25–218	P	(40, 62)

[1] CO_2 is included because of the hazard it may represent to those with CO_2 retention, such as those with advanced COPD.

those named in the third table. In addition to the epidemiological and pathological data gained from human studies, it is important to develop better bioassay systems to evaluate cigarettes modified by these general guidelines.

It should again be emphasized that, in addition to the variation in chemical properties of the cigarette being smoked, procedures within the control of the individual smoker such as how many cigarettes he smokes, how far down he smokes the cigarette, and how frequently and deeply he inhales are critical factors in determining how much of the harmful substances which can be produced by the burning cigarette is given the opportunity to injure him.

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